Interventional Cardiology

Comparison of vascular response to zotarolimus-eluting stent versus sirolimus-eluting stent: Intravascular ultrasound results from ENDEAVOR III

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Background The purpose of this study was to investigate the vascular response of zotarolimus-eluting stent (ZES) and sirolimus-eluting stent (SES) using serial intravascular ultrasound (IVUS).

Methods Data were obtained from the Endeavor Drug-Eluting Coronary Stent System Versus the Center Siromlimus-Eluting Coronary Stent System in De Novo Native Coronary Artery Lesions (ENDEAVOR) III trial, a randomized study comparing ZES and SES for the treatment of de novo native coronary artery lesions. Serial (baseline and 8-month follow-up) IVUS was available in 258 patients (190 ZES, 68 SES).

Results At 8 months, ZES had greater percentage of neointimal volume index (ZES 1.1 ± 0.8 mm^3/mm vs SES 0.2 ± 0.1 mm^3/mm, $P < .01$), resulting in smaller lumen volume index (6.0 ± 2.0 mm^3/mm vs 7.0 ± 2.1 mm^3/mm, $P < .05$). Zotarolimus-eluting stents showed larger IVUS-detectable neointimal coverage over stent surface (50.2% vs 10.5%, $P < .01$) and greater mean neointimal thickness (0.19 ± 0.07 mm vs 0.10 ± 0.06 mm, $P < .01$). Zotarolimus-eluting stents had a significantly lower incidence of late-acquired incomplete stent apposition.

Conclusions Zotarolimus-eluting stent is associated with a significantly greater amount of neointimal hyperplasia compared with SES. This amount of hyperplasia in ZES is distributed throughout the stent at 8-month follow-up. (Am Heart J 2008;155:108-13.)

Zotarolimus-eluting stent (ZES) (Medtronic Vascular Inc, Santa Rosa, CA) is a newly developed drug-eluting stent, which uses cobalt-based alloy, phosphorylcholine polymer, and zotarolimus (ABT-578, Abbott Pharmaceuticals, Abbott Park, IL). The aim of this study was to evaluate vascular response after ZES implantation compared with that after sirolimus-eluting stents (SES) using serial intravascular ultrasound (IVUS) analysis.

Methods

Patients

Data were derived from the Endeavor Drug-Eluting Coronary Stent System Versus the Center Siromlimus-Eluting Coronary Stent System in De Novo Native Coronary Artery Lesions (ENDEAVOR) III trial, a multicenter, single-blind, parallel, 2-arm, randomized control study comparing the efficacy between ZES and SES for the treatment of de novo coronary artery lesions.[1] Patients were randomized to either ZES or SES in a 3:1 fashion. The study protocol was approved by the institutional review board at each enrolling site; and consecutive, eligible patients signed written informed consent before the interventional procedure.

IVUS procedure and analysis

Intravascular ultrasound interrogation was planned for all subjects at postprocedure and at 8 months after stent implantation. The IVUS procedure was performed in a standard fashion using automated motorized 0.5 mm/s pullback with commercially available imaging systems (40-MHz IVUS catheter, Boston Scientific Corp, Natick, MA, or 20-MHz IVUS catheter, Volcano Corp, Rancho Cordova, CA). Intravascular ultrasound analysis was done in an independent core laboratory at Stanford University Medical Center (Cardiovascular Core Analysis Laboratory, Stanford, CA), blinded to the treatment arm. Incomplete stent apposition (ISA) was identified as one or more struts clearly separated from the vessel wall with evidence of blood speckles behind the strut. Incomplete stent apposition was classified as "persistent," "resolved," or "late acquired" as previously described.[2] All images were reviewed

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This study was supported by Medtronic Inc, Santa Rosa, CA.
Submitted April 6, 2007; accepted August 9, 2007.
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doi:10.1016/j.ahj.2007.08.008

Table I. Patient, lesion, and procedural characteristics

	ZES (n = 190)	SES (n = 68)	P
Age (y)	60.1 ± 9.8	60.3 ± 10.5	NS
Sex (male)	120 (60%)	56 (82%)	.02
Diabetes	57 (30%)	20 (29%)	NS
Hyperlipidemia	163 (85%)	59 (86%)	NS
Hypertension	127 (66%)	52 (76%)	NS
Smoking	124 (65%)	52 (76%)	NS
Previous myocardial infarction	34 (17%)	13 (19%)	NS
Class III/IV angina	98 (51%)	40 (58%)	NS
Target artery (LAD/LCX/RCA) (%)	46/23/31	40/31/29	NS
Lesion type (A/B1/B2/C) (%)	5/35/36/24	10/35/33/22	NS
Vessel reference (mm)	2.77 ± 0.45	2.79 ± 0.48	NS
Lesion length (mm)	14.45 ± 6.06	15.12 ± 6.67	NS
Max balloon pressure (atm)	13.4 ± 2.5	14.6 ± 3.0	<.01

NS, Not significant; *LAD*, left anterior descending coronary artery; *LCX*, left circumflex coronary artery; *RCA*, right coronary artery.

by 2 independent observers, and adjudication of opinion was based on consensus of these observers.

Volumetric measurements were performed using planimetry software (echoPlaque, Indec Systems Inc, Santa Clara, CA) as previously described.[3] Peristent plaque volume was calculated as vessel minus stent volume. Neointimal volume was calculated as stent minus lumen volume, and percentage (%) of neointimal obstruction was calculated as neointimal volume divided by stent volume. Neointimal coverage over stent surface and mean physical neointimal thickness were obtained by measuring circumferential stent length covered with neointimal hyperplasia (L_N) and stent perimeter (L_S) at every 1-mm cross-sectional image throughout the stented segment: (*a*) percentage of neointimal coverage over stent surface, calculated as total L_N divided by total L_S, and (*b*) mean physical neointimal thickness, calculated as mean neointimal area divided by mean L_N for only the cross sections with detectable neointima. *Detectable neointima* was defined as the presence of neointimal border clearly covering the stent strut surface observed by IVUS. This thickness calculation is theoretically more accurate than the conventional thickness calculation method, particularly when the stent has only focal or localized neointima. Conventional neointimal thickness was also calculated using stent and lumen areas with an assumption that neointima is completely concentric and evenly distributed along the stented segment.[4]

Statistical analysis

Statistical analysis was performed using Statview 5.0 (SAS Institute, Cary, NC). Continuous variables are expressed as mean ± SD. For continuous variables, comparisons between ZES and SES were performed with 2-tailed, unpaired *t* tests; and comparisons between baseline and follow-up were done by paired *t* test. Categorical variables were compared using χ^2 or Fisher exact test. Significance was assumed at a value of $P < .05$.

Results

Study population and patient characteristics

Intravascular ultrasound images were obtained in 296 cases (ZES 222, SES 74) at 8-month follow-up

Table II. Qualitative IVUS analysis

	ZES (n = 190)	SES (n = 68)	P
Dissection			
Proximal edge	2 (1.1%)	2 (2.9%)	NS
Distal edge	3 (1.5%)	2 (2.9%)	NS
Intraluminal tissue*	23 (12.1%)	21 (30.8%)	<.01
ISA			
ISA at baseline	24 (12.6%)	13 (19.1%)	NS
Resolved ISA	11	5	
Persistent ISA	13	8	
Late-acquired ISA	1 (0.5%)	4 (5.9%)	.02

*Intraluminal tissue may include thrombus and plaque prolapse.

analysis, with 258 cases (ZES 190, SES 68) available for serial (baseline and 8-month follow-up) analysis. Because of inconsistent pullback or inadequate image quality, 48 cases (ZES 35, SES 13) were excluded from volumetric analysis. Patient, lesion, and procedural characteristics are shown in Table I. Except for the higher percentage of men and the lower maximum balloon pressure in the ZES group, there were no significant differences between the 2 groups. There were no significant differences in baseline clinical/angiographic characteristics or follow-up angiographic outcomes between patients in and not in this IVUS substudy.

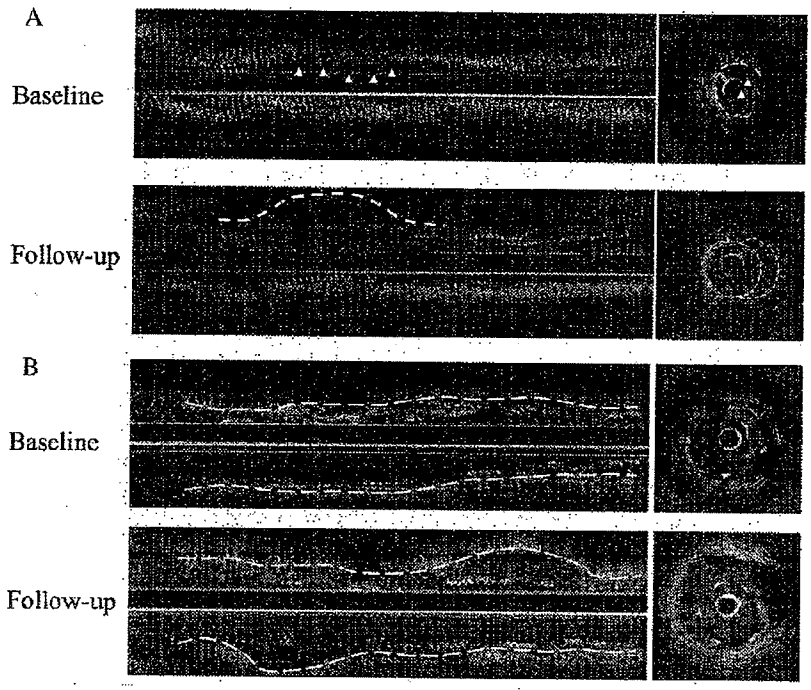
Qualitative analysis

Table II summarizes the result of qualitative analysis. In the ZES case with late-acquired ISA, intraluminal tissue was observed at baseline (Figure 1, *A*); and stent-vessel detachment at 8 months was observed at the site where intraluminal tissue had been detected (Figure 1, *A*). All late-acquired ISA cases in the SES group showed positive vessel remodeling (Figure 1, *B*). Among the 4 late-acquired ISA cases in SES, intraluminal tissue was observed in 1 case.

IVUS analysis—quantitative analysis

Follow-up volumetric analysis was possible in 248 cases (187 in ZES, 61 in SES). Among those cases, serial quantitative analysis was available in 164 cases (122 in ZES, 42 in SES) (Table III). Table IV summarizes the neointimal coverage over stent surface. Approximately 10% of stent surface was covered by IVUS-detectable neointimal tissue in SES, whereas significantly more stent surface was covered in ZES. Histogram of % neointimal obstruction demonstrated minimum neointimal obstruction in SES (Figure 2). The % neointimal obstruction of SES was <10% in almost all SES (2.7% ± 3.1%), whereas that of ZES ranged from 0% to 68% (16.1% ± 10.8%). In adjacent reference segments, IVUS indices did not show significant differences between baseline and follow-up or between the 2 groups (Table V).

Figure 1



Intravascular ultrasound images of late-acquired ISA. Longitudinal images are on the left side, and cross-sectional images at the most stent-vessel detachment are on the right. **A**, Late-acquired ISA in a ZES case. Intraluminal tissue is seen in baseline image (upper images, arrows). At follow-up, stent-vessel detachment is present where intraluminal tissue was observed at baseline (lower images). **B**, Late-acquired ISA in an SES case. Stent is well apposed at baseline (upper images). Stent-vessel detachment was associated with enlargement of external elastic membrane (dotted line).

Discussion

This IVUS analysis has shown that ZES had greater amount of neointima compared with SES. Zotarolimus-eluting stents also showed larger IVUS-detectable neointimal coverage over stent surface evenly distributed throughout its length and lower incidence of late-acquired ISA.

Immediate results

Platform material and stent design significantly affect the short-term mechanical properties of metallic stents. Zotarolimus-eluting stent is composed of a thin cobalt chromium alloy with an open-cell structure, whereas SES uses stainless steel with a closed-cell structure. Despite the difference in stent delivery system, our IVUS analysis showed that there was no significant difference in terms of volumetric measurements at postprocedure as well as qualitative parameters including edge dissections and baseline ISA. Unexpectedly, intraluminal tissue (plaque prolapse/intraluminal thrombus) was observed more frequently in SES. Factors including the difference in stent delivery systems and the higher maximum balloon pressure in SES may have contributed to this finding.

Neointimal formation at follow-up

The % neointimal obstruction of 16.1% of this trial is in accordance with previous clinical trials using ZES. ENDEAVOR II also showed 17.4% in ZES as compared with 29.4 % with bare-metal stents.[5] With regard to volumetric IVUS analysis, % neointimal obstruction, calculated as neointimal volume divided by stent volume, has been shown to have a uniquely consistent value for each stent type. This value presumably represents the performance of each drug-eluting stent for neointimal inhibition, reported as 29% to 35% in bare-metal stents,[6] 8% to 13% in polymer-based paclitaxel-eluting stents (PES),[7,8] and 3% to 5% in SES.[6,9] The magnitude of neointimal volume alone, however, may not equally implicate the effectiveness of drug-eluting stents. Previous IVUS studies have shown relatively higher %

Table III. Intravascular ultrasound measurements in stent segment

	ZES (n = 122)		SES (n = 42)	
	Baseline	**Follow-up**	**Baseline**	**Follow-up**
LV index (mm^3/mm)	7.0 ± 2.1*	6.0 ± 2.0*	6.8 ± 2.1	6.8 ± 2.0
VV index (mm^3/mm)	13.7 ± 4.3	14.2 ± 4.3	11.9 ± 4.1	12.6 ± 4.1
PV index (mm^3/mm)	6.7 ± 2.7	7.0 ± 2.7	5.8 ± 2.7	6.2 ± 2.7
NIV index (mm^3/mm)		1.1 ± 0.8†		0.2 ± 0.1†
% NIV obstruction		16.1 ± 10.8†		2.7 ± 3.1†

% NIV obstruction was calculated as neointima volume within the stent divided by the overall stent volume. *LV*, Lumen volume; *VV*, vessel volume; *PV*, peristent plaque volume; *NIV*, neointima volume.
*P = .03 (baseline vs follow-up).
†P < .01 (ZES vs SES).

Table IV. Neointimal coverage and neointimal thickness

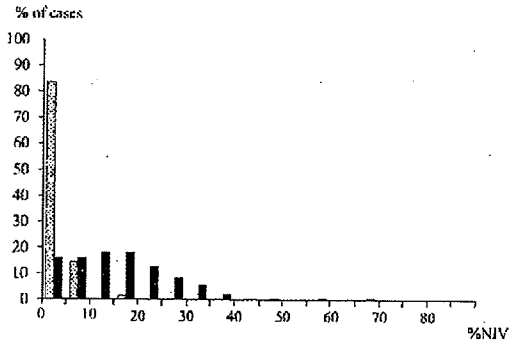
	ZES (n = 187)	SES (n = 61)	P
NI covered area over stent surface (%)	50.21 ± 25.95	10.45 ± 11.70	<.01
Mean physical NI thickness (mm)	0.19 ± 0.07	0.10 ± 0.06	<.01
Mean NI thickness (mm)	0.26 ± 0.19	0.04 ± 0.04	<.01

NI, Neointima.

neointimal obstruction in PES as compared with SES, although clinical event rates in PES were similar to SES. Weissman et al described that in-stent neointima in PES may be below the threshold of physiologic significance in most patients.[7] Although the % neointimal obstruction presumably represents the power of a drug-eluting stent for neointimal inhibition, it remains an open question whether there is acceptable range of neointimal growth.

Our measurements inside the stent revealed different nature of neointimal hyperplasia in ZES. Whereas neointimal volume in ZES is 8 times as much as that seen in SES, mean physical neointimal thickness showed only around 2 times as much as that in SES. In addition, the mean physical thickness is only 0.19 mm in ZES, which can be considered to be minimal in terms of lumen diameter loss. Zotarolimus-eluting stents also showed larger IVUS-detectable neointimal coverage over stent surface compared with SES. This result suggested that neointimal formation in ZES was evenly distributed in contrast to focal neointimal formation seen in SES. With focal accumulation of neointimal tissue, even small amount of neointima can encroach luminal space, possibly leading to significant late loss. In other words, even when there is the same amount of neointimal hyperplasia, neointimal tissue distributed focally can encroach more than that distributed evenly and diffusely

Figure 2



Statistical distribution of percentage of neointimal volume. Light gray bars: SES; black bars: ZES.

within the stent. Distributed nature of neointima in ZES may contribute to minimizing the luminal loss (ie, physical neointimal thickness), despite relatively larger amount of neointima. Although the clinical impact of neointimal characteristics should be confirmed by longer observation, supplementary analysis, such as neointimal coverage or thickness, would be necessary for a better understanding of the properties of drug-eluting stent.

It is unknown whether the IVUS-detectable neointimal coverage is associated with any clinical outcome. To minimize the risk of stent thrombosis, it would be desirable for drug-eluting stents to allow an adequate amount of reendothelialization without compromising lumen dimension.[10] In the present study, more than half of the stent struts of ZES were covered by IVUS-detectable neointimal hyperplasia, whereas only approximately 10% of stent struts were covered in SES. Although longer follow-up and careful clinical observations are clearly needed, it should be determined whether certain amount of neointimal coverage relates to safety profile. So far, there is no documented association between adverse cardiac events and the absence of IVUS-detectable intimal hyperplasia.

Late-acquired ISA

Previous studies have shown the incidence of late-acquired ISA to be from 3% to 13% in SES[2,11,12] and from 2% to 8% in PES.[12,13] This IVUS analysis confirmed the similar incidence of late-acquired ISA in SES, while demonstrating a significantly lower incidence of late-acquired ISA with ZES. In addition, throughout the entire ENDEAVOR trial series (I, II, III, Continued Access), this is the only case of late-acquired ISA in ZES thus far. In this particular case, late-acquired ISA was associated with thrombus on both inside and outside the stent at baseline; and apparent positive vessel remodeling was not observed.

Table V. Intravascular ultrasound measurements in proximal and distal adjacent segments

	SES (n = 42)			ZES (n = 122)		
Reference	**Baseline**	**Follow-up**	***P***	**Baseline**	**Follow-up**	***P***
Proximal (mm^3/mm)						
LV index	7.8 ± 2.6	7.2 ± 2.6	NS	6.4 ± 2.9	7.2 ± 3.1	NS
VV index	13.5 ± 4.8	13.5 ± 4.4	NS	13.0 ± 5.6	12.8 ± 5.4	NS
PV index	5.7 ± 2.5	6.1 ± 2.5	NS	6.4 ± 3.5	5.7 ± 2.2	NS
Distal (mm^3/mm)						
LV index	6.5 ± 2.5	6.1 ± 2.2	NS	5.7 ± 2.4	5.7 ± 2.5	NS
VV index	10.5 ± 4.6	10.4 ± 4.4	NS	9.7 ± 4.8	9.1 ± 5.1	NS
PV index	4.1 ± 2.7	4.3 ± 2.8	NS	3.9 ± 2.7	3.6 ± 2.4	NS

Although late-acquired ISA has not been proven to be associated with any clinical sequelae, this IVUS finding has been a concern as a possible underlying mechanism of future clinical events including late thrombosis.[14] In the current study, all late-ISA cases in SES showed significant vessel enlargement at the stent-vessel detachment site. In a detailed report from 14 autopsies of stent thrombosis, the main characteristics of pathology seen in these late-stent thrombosis cases include local hypersensitivity, ostial/bifurcation stenting, ISA, restenosis, and strut penetration into a necrotic core.[15] The IVUS features of late-acquired ISA (ie, positive vascular remodeling and unattached stent struts) appear analogous to the pathology observed in stent thrombosis. Because the exact mechanism of late-acquired ISA is still being clarified, further observation across the different types of drug-eluting stent and careful long-term follow-up of such cases should be mandated.

Limitations

Several limitations should be noted. First, a portion of enrolled patients failed to receive IVUS, thus posing a risk for selection bias. Furthermore, the findings of this article were derived from the patients who were able to receive IVUS at follow-up, potentially leading to a risk for selection bias. Second, because of limited IVUS resolution (>80 μm axially and 200 μm laterally), endothelialization on stent surface may not be fully visualized. Hence, IVUS-estimated neointimal coverage over stent surface in this study may not fully explain the profile regarding stent thrombosis. Third, there are differences in the design, length, and appearances between the 2 studied stents. Although in most of the cases it was not possible to speculate the stent types based on the IVUS images, these differences may potentially have compromised the blinded nature. Fourth, the unbalanced randomization resulted in a relatively small number of SES patients in the comparison group; therefore, results for SES were subject to potential overinterpretation due to broad CIs. Finally, there are some intrinsic limitations, such as image reconstruction or image interpretation, to IVUS analysis as previously reported.[3]

Conclusions

Detailed IVUS observations from ENDEAVOR III showed different neointimal characteristics at 8-month follow-up between SES and ZES. Despite greater neointimal volume in ZES, distinctive neointimal characteristics, such as distributed neointimal growth and modest neointimal thickness, might contribute to clinically acceptable lumen loss. Combined with less late-acquired ISA, the larger neointimal coverage over the stent surface may have contributed to the safety profile in terms of late thrombosis.

We thank Heidi N. Bonneau, MS, RN, for her expert review of this manuscript.

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A randomized, double-blind, placebo-controlled study of the safety and efficacy of intravenous MCC-135 as an adjunct to primary percutaneous coronary intervention in patients with acute myocardial infarction: Evaluation of MCC-135 for left ventricular salvage in acute myocardial infarction (EVOLVE)

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Objectives The objective of the study was to test the hypothesis that intracellular calcium modulation by 5-methyl-2-[piperazin-1-yl] benzene sulfonic acid monohydrate (MCC-135 [Caldaret]; Mitsubishi Pharma Corporation, Osaka, Japan) would preserve left ventricular function and reduce infarct size in patients undergoing primary percutaneous coronary intervention (PCI) for ST-elevation myocardial infarction (STEMI).

Background Calcium overload inside myocytes during ischemia and reperfusion not only affects myocardial function but also may be related to myocyte necrosis. MCC-135 is the first in a new class of agents that modulate intracellular calcium overload.

Methods Patients with acute STEMI undergoing primary PCI were randomized into placebo, low-dose, and high-dose MCC-135 groups. The predefined target population was those with anterior myocardial infarction and pre-PCI TIMI grade flow 0 or 1. Left ventricular ejection fraction (LVEF) on Day 5 was the primary end point. Secondary end points included infarct size measured by single photon emission computed tomography and by serum cardiac markers. Patients were followed up to 30 days for clinical outcome.

Results Among 500 patients enrolled, 141 qualified as the target population. In this target population, there was no difference in the LVEF between 3 groups (placebo: 47.0% ± 1.7% [mean ± SEM], the low dose: 47.4% ± 1.7%, the high dose: 45.1% ± 2.0%). The infarct size on day 5 was not significantly different between the groups. The composite clinical outcome occurred in 25.5% in the placebo group, in 19.2% in the low-dose group, and in 34.2% in the high-dose group during a 30-day follow-up period (P = nonsignificant). MCC-135 appeared to be safe and well tolerated.

Conclusion There were no significant benefits of MCC-135 on preservation of LVEF and reduction of infarct size on day 5 in patients with STEMI undergoing primary PCI. (Am Heart J 2008;155:113.e1-113.e8)

European Heart Journal (2007) 28, 1583–1591
doi:10.1093/eurheartj/ehl423

Clinical research
Interventional cardiology

Clinical impact of in-stent late loss after drug-eluting coronary stent implantation†

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Received 8 April 2006; revised 22 October 2006; accepted 10 November 2006; online publish-ahead-of-print 8 February 2007

KEYWORDS
Number of patients needed to treat;
Drug-eluting stents;
Restenosis

Aims Controversy exists about the clinical significance of in-stent late loss (ISLL) after drug-eluting stent (DES) implantation. We sought to clarify whether ISLL after DES implantation is related to a potential clinical impact.

Methods and results We included in a meta-regression analysis 21 trials (8641 patients) that randomly compared DES with bare-metal stents (BMS). We evaluated the relationship between angiographic behaviour of DES and the clinical impact of using DES instead of BMS in each trial using meta-regression techniques, weighting by the number of patients included in each trial. Mean ISLL in patients allocated to DES and ΔISLL (difference in ISLL in patients allocated to BMS and DES) were used as angiographic parameters of efficacy of DES. The number of patients needed to be treated (NNT) to prevent one target lesion revascularization (TLR) was used to quantify the clinical impact of using DES instead of BMS. There was a significant relationship between mean ISLL in patients allocated to DES and the clinical benefit of using DES instead of BMS, as measured with the NNT for TLR: NNT for TLR = 6.2 + 18.4 [ISLL-DES] ($R = 0.62$; $P = 0.007$). Therefore, a 0.1 mm increase in mean ISLL-DES was associated with a 1.8 increase in NNT for TLR. There was also a significant association between the degree of inhibition of neointimal hyperplasia of DES in comparison with BMS with the NNT for TLR: NNT for TLR = 17.1–11.8 [ΔISLL] ($R = 0.61$; $P = 0.008$). Therefore, a 0.1 mm reduction in ISLL by using DES instead of BMS was associated with a 1.2 decrease in mean NNT for TLR.

Conclusion There is a strong and significant association between the degree of inhibition of neointimal formation with the use of DES and the clinical impact of using DES instead of BMS.

Introduction

In-stent restenosis due to neointimal formation is the main limitation of bare-metal stents (BMS), as it frequently leads to subsequent revascularization procedures.[1] Drug-eluting stents (DES) dramatically reduce both angiographic restenosis and the need for new revascularization procedures by means of inhibiting the formation of neointimal hyperplasia within the stent.[2–20]

In-stent late loss (ISLL) is a frequently used parameter to quantify the degree of neointimal hyperplasia after coronary stenting.[21] It is simple, easy to understand, and very intuitive. ISLL reflects the biological activity of a DES, and currently, it is being used to compare the efficacy of different types of DES in different randomized trials.

Despite all these considerations, the idea that mean ISLL after DES implantation has only limited clinical impact, especially among the range of 0–0.5 mm, has been accepted by many interventional cardiologists, even proposing that only when mean ISLL is higher than 0.5 mm there is a clear increase in the need for new revascularizations.[22] This theory is mainly based on rather similar rates of new revascularization procedures after paclitaxel-eluting stent (PES) and sirolimus-eluting stent (SES) implantation despite mean ISLL after PES being approximately two-fold higher than after SES stenting. Additionally, different mean ISLLs have not been translated into different clinical outcomes in some very recent trials that have compared different types of DES.[22]

The objective of the present study was to clarify whether mean ISLL is related to the clinical impact of using DES instead of BMS. We hypothesized that ISLL is of clinical significance, and that differences in mean ISLL translate into differences in clinical outcome, even within the range of

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† Presented in part at the Scientific Sessions of the American Heart Association, Dallas, TX, USA, November 2005.

0–0.5 mm. To test this hypothesis, we performed a meta-regression analysis from randomized trials that have compared DES with BMS. Since the number needed to treat (NNT) is probably the most precise parameter for measuring the clinical benefit associated with a given therapeutic strategy, we evaluated the relationship between mean ISLL and the NNT for new revascularizations.

Methods

Selection of the studies

In order to identify the trials to be included in the study, we conducted a computerized bibliographic search of the MEDLINE database (National Library of Medicine, Bethesda, MD, USA) and in the abstract supplements of four major scientific meetings—European Society of Cardiology, American College of Cardiology, American Heart Association, and Transcatheter Cardiovascular Therapeutics—until January 2006. We selected all the randomized trials that compared DES and BMS and that provided both follow-up angiographic data and the rate of target lesion revascularization (TLR) for patients allocated to DES and BMS. We included only trials in which coronary stents commercially available in Europe by 2006 were evaluated. We included 21 randomized trials that evaluated the following DES: (i) The SES Cypher (Cordis Corp.): RAVEL, SIRIUS, E-SIRIUS, C-SIRIUS, DIABETES, SCANDSTENT, SES-SMART, STRATEGY, PRISON-II, and the study by Pache *et al.*;[19] (ii) The PES Taxus (Boston Sci.): TAXUS-I, TAXUS-II, TAXUS-IV, TAXUS-V, and TAXUS-VI. As the TAXUS-II evaluated two different release kinetics of paclitaxel (slow-release and moderate-release), each of them with a control group of patients, we analysed these two sub-studies separately; (iii) The tacrolimus-eluting stent (TES) Janus (Sorin Biomedica): JUPITER-II study; (iv) The zotarolimus-eluting stent (ZES) Endeavor (Medtronic Inc.): ENDEAVOR-II trial; and (v) The everolimus-eluting stent (EES, currently the Xience V stent, Guidant Corp.): FUTURE-I, FUTURE-II, and SPIRIT-I trials.[2–20]

Out of the 21 trials included, two were performed in a single centre, and 19 were multicentred. The blinding of the trial was double in most of the trials, although it was single in SES-SMART, STRATEGY, DIABETES, FUTURE-I, FUTURE-II, SPIRIT-I, and the study by Pache *et al.*[10] Blinding was maintained at quantitative coronary analysis during angiographic follow-up.

Figure 1 shows a patient flow diagram including the number of patients randomized, the number of patients that received standard therapy as allocated, and the number of patients that were followed-up both for BMS and DES arms. Analysis was performed in an intention-to-treat basis in all the trials included. Overall, 8641 patients were randomized (4320 allocated to BMS and 4321 to DES). The proportion of patients that received standard intervention as allocated was similar for BMS and DES (98.7 vs. 98.7%, respectively; $P = 0.777$), and the proportion of patients that were followed-up for primary endpoint was similar for both groups (95.0 vs. 95.2%, respectively; $P = 0.752$). *Table 1* shows the number of patients included in each study, as well as the main clinical and angiographic characteristics of the population included in the trials.

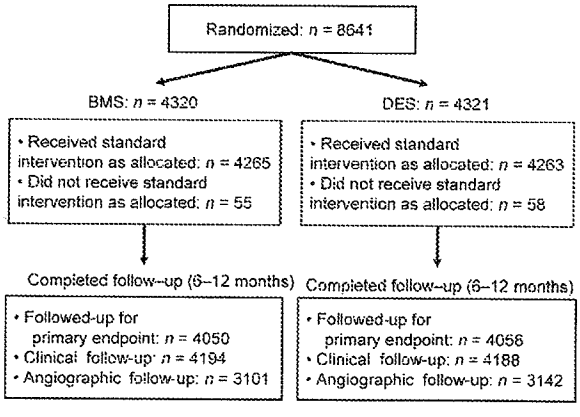

Figure 1 Patient flow diagram.

Definitions and statistical analysis

ISLL was defined as the difference between minimum lumen diameter (MLD) immediately after coronary stent implantation and that obtained at angiographic follow-up, both in DES and BMS groups. As mean values were provided in the trials included, we used the mean value of each trial for the statistical analysis. ΔISLL was calculated as the difference between mean ISLL in patients allocated to BMS and mean ISLL in those allocated to DES in each trial, and reflects the degree of inhibition of neointimal hyperplasia by using DES instead of BMS in each of the studies included.

We used the NNT for new TLR procedures as a measurement of the clinical benefit of using DES instead of BMS in each trial. The NNT is the number of patients who need to be treated in order to prevent one adverse outcome. It is the inverse of the absolute risk reduction (ARR) and was calculated as 1/ARR. ARR was calculated as the difference in the rate of TLR between the control group and the patients allocated to DES in each trial. Although the NNT is usually reported rounded to the next higher whole number, we maintained one decimal for statistical purposes.

The pooled estimates were obtained using the Peto's Assumption Free Method for Combining Trials, and the heterogeneity between groups was assessed by the Q-statistics. The correlation test of Begg and the regression-based test of Egger were used to assess the possible existence of publication bias.

As the objective of the study was to evaluate the relationship between the clinical benefit of using DES instead of BMS (NNT for TLR), head-to-head trials comparing different types of DES were not included for the evaluation of the influence of mean ISLL on the clinical impact of using DES instead of BMS. However, these trials were included when evaluating the relationship between mean ISLL and TLR in each group of patients treated with the same stent in each trial. The head-to-head trials included in this analysis are shown in *Table 2*, and include the following: SIRTAX, REALITY, ISAR-DESIRE, ISAR-DIABETES, ISAR-SMART-3, CORPAL, ISAR-TEST, and ENDEAVOR-III.[23–30]

Associations between angiographic data (mean ISLL and ΔISLL) and both the incidence of TLR and the clinical benefit of using DES instead of BMS (NNT for TLR) were evaluated by linear regression ($Y = \alpha + \beta X$), weighting all these associations by the number of patients included in each trial; 95% confidence intervals (CI) for the β coefficient are provided. Associations were considered statistically significant when the two-tailed *P*-value was lower than 0.05. The SPSS 12.0 statistical package was used (Chicago, IL, USA).

Results

Characteristics of the trials included

No publication bias was detected (Begg's test: $P = 0.484$; Eggeŕs test: $P = 0.137$).

Table 1 shows the main angiographic and clinical baseline characteristics of the trials included. Mean reference vessel diameter (RVD) at baseline ranged from 2.20 mm (SES-SMART) to 3.05 mm (FUTURE-I), and lesion length from 9.6 mm (RAVEL) to 20.6 mm (TAXUS-VI). The proportion of diabetic patients ranged from 2 to 100%.

Table 1 Main clinical and angiographic baseline characteristics of the trials included in the meta-analysis

Trial	*N*	DES	Primary endpoint	Age (years)	Female (%)	DM (%)	RVD (mm)	MLD (mm)	Length (mm)
RAVEL	238	SES	ISLL	61	24	19	2.62	0.94	9.6
SIRIUS	1101	SES	Target vessel failure	62	29	26	2.80	0.98	14.4
E-SIRIUS	353	SES	In-stent MLD	62	29	23	2.55	0.88	15.0
C-SIRIUS	102	SES	In-stent MLD	61	29	24	2.63	0.80	13.6
SCANDSTENT	322	SES	Difference in-lesion MLD	63	24	18	2.86	0.65	18.0
DIABETES	160	SES	ISGLL	66	37	100	2.34	0.90	15.0
SES-SMART	257	SES	BAR	64	28	25	2.20	0.72	11.8
STRATEGY	175	SES	MACE	63	36	13	2.30	0.0	13.1
Pache *et al.*[10]	500	SES	BAR	67	22	31	2.70	–	12.6
PRISON-II	200	SES	BAR	59	20	13	3.32	0.0	16.2
TAXUS-I	61	PES	MACE	65	12	18	2.97	1.27	11.3
TAXUS-II-SR	267	PES	Volume obstruction (IVUS)	61	26	14	2.80	0.93	10.6
TAXUS-II-MR	269	PES	Volume obstruction (IVUS)	59	24	16	2.70	2.73	10.5
TAXUS-IV	1326	PES	Target vessel revascularization	62	28	24	2.75	0.94	13.4
TAXUS-V	1172	PES	Target vessel revascularization	63	31	31	2.69	0.86	17.3
TAXUS-VI	446	PES	Target vessel revascularization	63	24	30	2.79	0.86	20.6
ENDEAVOR-II	1197	ZES	Target vessel failure	62	24	20	2.75	0.83	14.2
FUTURE-I	42	EES	ISLL	65	14	2	3.05	1.12	8.9
FUTURE-II	61	EES	ISLL	63	30	27	2.95	1.04	11.4
SPIRIT-I	60	EES	ISLL	63	27	11	2.66	–	10.5
JUPITER-II	332	TES	ISLL	64	24	19	–	1.03	12.1

DM, diabetes mellitus; IVUS, intravascular ultrasound; MACE: major adverse cardiac events.

Table 2 Main clinical and angiographic data from head-to-head trials comparing different types of DES

Trial	Stent	*N*	Age (years)	Female (%)	DM (%)	RVD (mm)	MLD (mm)	Length (mm)	TLR	BAR	ISLL	ISGLL
SIRTAX	SES	503	62	22	14	2.82	0.52	11.8	4.8	3.2	0.12	–
	PES	509	62	18	12	2.82	0.53	12.4	8.3	7.5	0.25	–
REALITY	SES	684	63	26	27	2.40	0.91	17.0	5.0	7.0	0.09	0.04
	PES	669	63	28	29	2.40	0.91	17.3	5.4	8.3	0.31	0.16
ISAR-DESIRE	SES	100	63	22	31	2.60	0.91	12.4	8.0	11.0	0.10	0.32
	PES	100	65	21	27	2.60	0.97	11.5	19.0	18.5	0.26	0.55
ISAR-DIABETES	SES	125	68	32	100	2.70	1.03	13.8	6.4	4.9	0.19	–
	PES	125	68	36	100	2.75	1.12	12.4	12.0	13.6	0.46	–
ISAR-SMART-3	SES	180	67	55	0	2.44	0.99	12.9	6.6	8.0	0.25	0.13
	PES	180	66	45	0	2.40	1.03	11.7	14.7	14.9	0.56	0.34
CORPAL	SES	331	60	22	29	2.96	–	26.0	5.7	12.4	–	0.36
	PES	321	62	25	33	2.94	–	24.0	9.0	18.6	–	0.54
ISAR-TEST	Yukon	225	67	25	32	2.72	1.14	12.6	9.3	12.6	0.48	0.34
	PES	225	67	21	26	2.73	1.14	12.9	9.3	11.6	0.48	0.24
ENDEAVOR-III	ZES	323	61	35	30	2.75	0.92	15.0	6.3	9.2	0.60	0.34
	SES	113	62	19	28	2.79	0.90	15.0	3.5	2.1	0.15	0.13

DM, diabetes mellitus.

Relationship between ISLL and TLR

There was a significant and strong association between mean ISLL and the proportion of patients undergoing TLR in each allocated group in each trial in trials that randomly compared DES with BMS (*Figure 2*): TLR = 2.8 + 18.1 (ISLL) ($R = 0.82$; 95% CI for β: 13.9, 22.3; $P < 0.001$). When including also the groups of patients included in head-to-head trials comparing different types of DES, the association between mean ISLL and TRL remained strong and significant: TLR = 4.0 + 16.1 (ISLL) ($R = 0.78$; 95% CI for β: 12.5, 19.8; $P < 0.001$). When including only those allocated groups of patients in which mean ISLL was <0.5 mm, the relationship between mean ISLL and TLR remained statistically significant: TLR = 3.7 + 10.0 (ISLL) ($R = 0.40$; 95% CI for β: 1.0, 18.9; $P = 0.030$).

There was also a significant association between the proportion of patients with binary angiographic restenosis (BAR) and the rate of TLR: TLR = 3.38 + 0.48 [BAR] ($R = 0.86$; 95% CI for β: 0.39, 0.57; $P < 0.001$). When including also data from the head-to-head trials comparing different types of DES, the linear regression was very similar: TLR = 3.3 + 0.48 [BAR] ($R = 0.85$; 95% CI for β: 0.40, 0.56; $P < 0.001$).

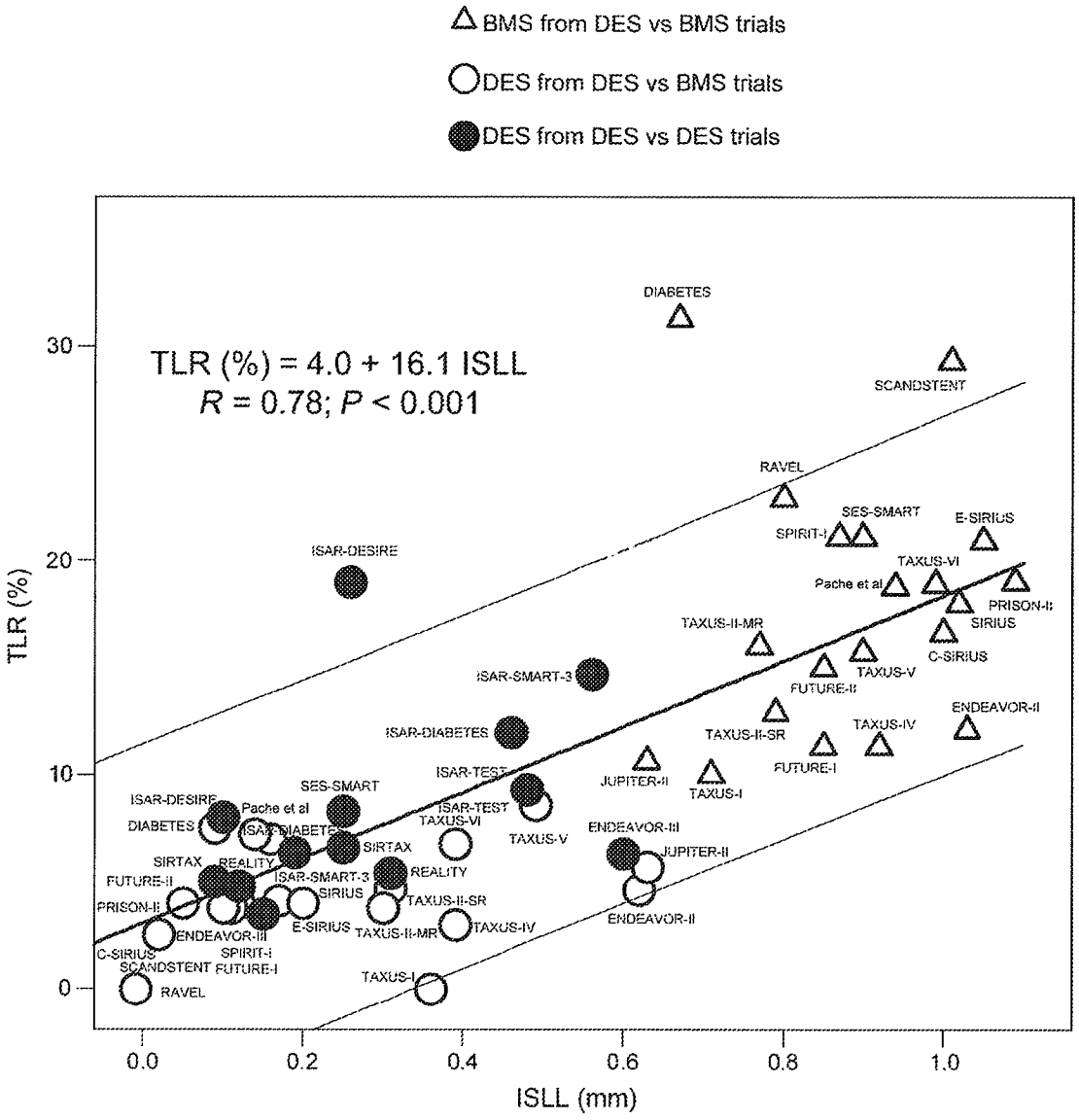

Figure 2 Relationship between ISLL and TLR in each treatment group in randomized trials that have evaluated DES. The figure displays data from randomized trials comparing DES and BMS, and also from head-to-head studies comparing different types of DES.

Benefit of using DES instead of BMS

Data on mean ISLL for each study are shown in *Table 3*. In all trials except the JUPITER-II, mean ISLL was significantly lower in patients allocated to DES. Mean ISLL ranged from 0.63 to 1.09 mm in patients allocated to BMS, and from −0.01 to 0.63 mm in those allocated to DES. ΔISLL ranged from 0.00 to 1.04 mm.

Rates of BAR, TLR, as well as the calculated NNT for each of these endpoints are also reported in *Table 3*. In all the trials, BAR occurred less frequently in patients allocated to DES, but the degree of clinical benefit (NNT) widely varied among the studies. NNT for binary restenosis ranged from 2.2 to 15.6, and NNT for TLR from 3.7 to 22.2. *Figure 3* shows mean data of ISLL in patients allocated to DES, and angiographic (ΔISLL and NNT for BAR), and clinical benefit (NNT for TLR) of using DES instead of BMS. Among all the types of DES evaluated in the trials included, the SES stent showed the highest ΔISLL, and the lowest NNT for both BAR and TLR. In contrast, the TES stent showed the lowest ΔISLL, and the highest NNT for both BAR and TLR.

Relationship between mean ISLL and the clinical impact of using DES

There was a significant relationship between mean ISLL in patients allocated to DES and the clinical benefit of using DES instead of BMS, as measured with the NNT for TLR (*Figure 4*): NNT for TLR = 6.2 + 18.4 [ISLL-DES] ($R = 0.62$; 95% CI for β: 5.8, 31.0; $P = 0.007$). Therefore, a 0.1 mm increase in

Table 3 Follow-up angiographic data in the trials included in the meta-analysis

	BAR (%)			TLR (%)			ISLL (mm)			ISGLL (mm)		
	DES	BMS	NNT	DES	BMS	NNT	DES	BMS	Δ	DES	BMS	Δ
RAVEL	0.0	26.6	3.8	0.0	22.9	4.4	−0.01	0.80	0.81	–	–	–
SIRIUS	3.2	35.4	3.1	4.1	16.6	8.0	0.17	1.00	0.83	0.24	0.81	0.57
E-SIRIUS	3.9	41.7	2.6	4.0	20.9	5.9	0.20	1.05	0.85	0.19	0.80	0.61
C-SIRIUS	0.0	45.5	2.2	4.0	18.0	7.1	0.12	1.02	0.90	0.12	0.79	0.67
SCANDSTENT	2.0	30.6	3.5	2.5	29.3	3.7	0.02	1.01	0.99	0.04	0.94	0.90
DIABETES	3.9	31.7	3.6	7.5	31.3	4.2	0.09	0.67	0.58	0.06	0.47	0.41
SES-SMART	4.9	49.1	2.3	7.0	21.1	7.1	0.16	0.90	0.74	0.16	0.69	0.53
STRATEGY	7.5	28.0	4.9	5.7	20.5	6.8	–	–	–	−0.22	0.60	0.82
Pache *et al.*[10]	8.3	25.5	5.8	7.2	18.8	8.6	0.14	0.94	0.80	–	–	–
PRISON-II	7.0	36.0	3.4	4.0	19.0	6.7	0.05	1.09	1.04	−0.07	0.64	0.71
TAXUS-I	0.0	10.3	9.7	0.0	10.0	10.0	0.36	0.71	0.35	–	–	–
TAXUS-II-SR	2.3	17.9	6.4	4.7	12.9	12.2	0.31	0.79	0.48	–	–	–
TAXUS-II-MR	4.7	20.2	6.5	3.8	16.0	8.2	0.30	0.77	0.47	–	–	–
TAXUS-IV	5.5	24.4	5.3	3.0	11.3	12.0	0.39	0.92	0.53	0.23	0.61	0.38
TAXUS-V	13.7	31.9	5.5	8.6	15.7	14.1	0.49	0.90	0.41	0.33	0.60	0.27
TAXUS-VI	9.1	32.9	4.2	6.8	18.9	8.3	0.39	0.99	0.60	–	–	–
ENDEAVOR-II	9.5	32.7	4.3	4.6	12.1	13.3	0.62	1.03	0.41	–	–	–
FUTURE-I	0.0	9.1	11.0	3.8	8.3	22.2	0.11	0.85	0.74	–	–	–
FUTURE-II	0.0	19.4	5.2	4.8	15.0	9.8	0.12	0.85	0.73	0.17	0.54	0.37
SPIRIT-I	0.0	25.9	3.9	3.8	21.1	5.8	0.12	0.89	0.77	0.07	0.61	0.54
JUPITER-II	9.4	15.8	15.6	5.7	10.6	20.4	0.63	0.63	0.00	0.40	0.44	0.04

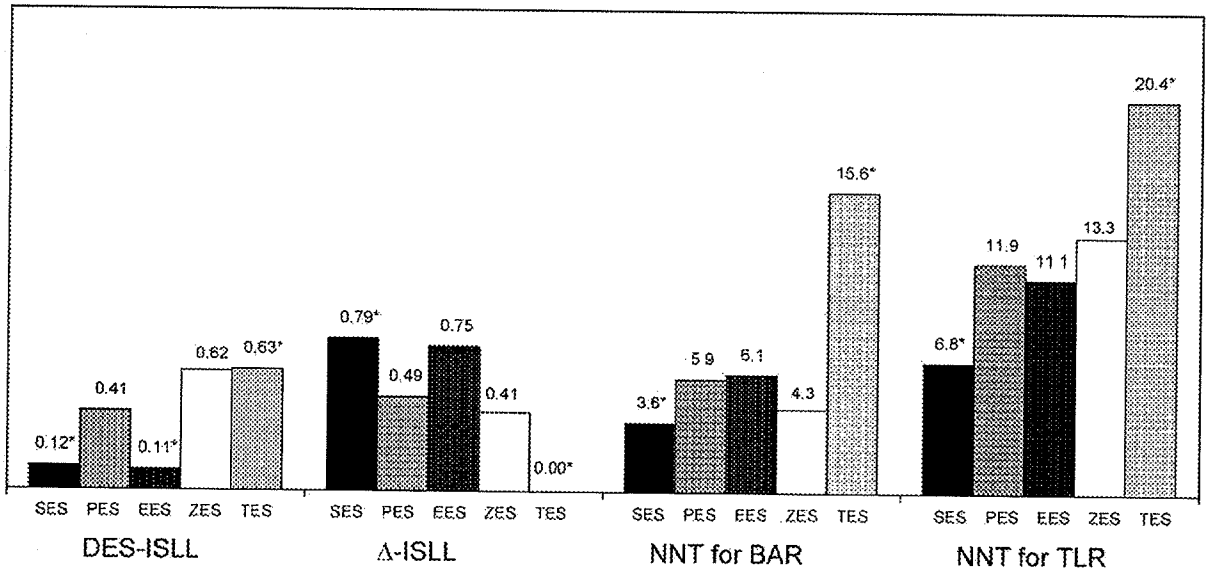

Figure 3 Angiographic (ISLL in patients allocated to DES, ΔISLL, and NNT for BAR) and clinical (NNT for TLR) benefit of using DES instead of BMS for each type of DES evaluated in the trials included in the meta-analysis. *$P < 0.05$.

ISLL-DES was associated with a 1.8 increase in NNT for TLR. The association remained significant after adjusting by the proportion of diabetic patients (NNT for TLR = 8.0 + 17.3 [ISLL-DES]−0.002 [% of diabetics]; $R = 0.66$; 95% CI for β: 4.9, 25.1; $P = 0.006$), by the mean RVD (NNT for TLR = −11.7 + 12.0 [ISLL-DES] + 6.6 [mean RVD]; $R = 0.59$; 95% CI for β: 1.1, 23.1; $P = 0.034$) or the mean lesion length in each trial (NNT for TLR = 13.7 + 17.2 [ISLL-DES]−0.6 [mean lesion length]; $R = 0.70$; 95% CI for β: 7.5, 26.8; $P = 0.002$).

When considering the degree of reduction of neointimal hyperplasia associated with the use of DES instead of BMS (ΔISLL) as independent variable, there was a significant association between ΔISLL and the clinical benefit of using DES instead of BMS (*Figure 5*): NNT for TLR = 17.1 − 11.8 [ΔISLL] ($R = 0.61$; 95% CI for β: −20.1, −3.6; $P = 0.008$). Therefore, a 0.1 mm increase in ΔISLL (a 0.1 mm reduction in mean ISLL by using DES instead of BMS) is associated with a 1.2 decrease in NNT for TLR. Using ΔISLL instead of

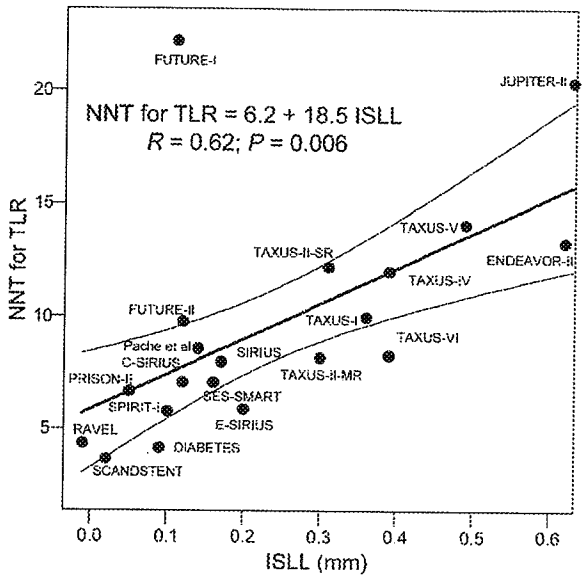

Figure 4 Relationship between the ISLL in patients allocated to DES, and the number of patients needed to prevent one TLR in each trial. Results are adjusted by the number of patients included in each trial.

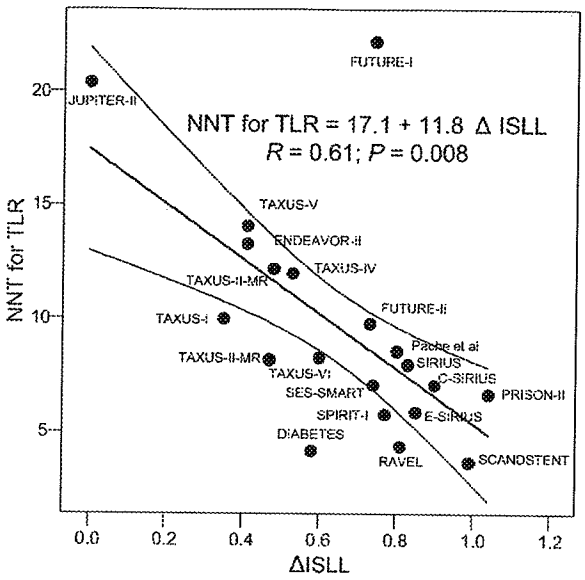

Figure 5 Relationship between the reduction of ISLL in patients allocated to DES in comparison with those allocated to BMS (ΔISLL), and the number of patients needed to prevent one TLR in each trial. Results are adjusted by the number of patients included in each trial.

ISLL has the advantage of adjusting by the ISLL in patients allocated to BMS in each study. This association remained statistically significant after adjusting by the proportion of diabetic patients (NNT for TLR = 23.3 - 12.7 [ΔISLL] - 1.0 [% of diabetics]; $R = 0.72$; 95% CI for β: -19.7, -5.7; $P = 0.001$), the mean RVD (NNT for TLR = -5.1 - 10.8 [ΔISLL] + 7.8 [mean RVD]; $R = 0.61$; 95% CI for β: -19.8, -1.7; $P = 0.023$) or the mean lesion length in each trial (NNT for TLR = 21.2 - 11.5 [ΔISLL] - 0.31 [mean lesion length]; $R = 0.64$; 95% CI for β: -19.4, -3.6; $P = 0.007$).

When using in-segment late loss (ISGLL) instead of ISLL as angiographic parameter, the clinical implications of differences in ISGLL were also significant: NNT for TLR = 5.8 + 19.1 [ISGLL in DES] ($R = 0.71$; 95% CI for β: 2.8, 35.4; $P = 0.026$); and NNT for TLR = 15.8 - 15.2 [delta ISGLL in DES] ($R = 0.84$; 95% CI for β -23.2, -7.3; $P = 0.002$).

There was also a significant and strong association between the NNT for BAR and the NNT for TLR in each trial: NNT for TLR = 1.01 + 1.28 [NNT for BAR] ($R = 0.86$; 95% CI for β: 0.89, 1.66; $P < 0.001$).

Discussion

Benefit of DES over BMS

The leading mechanism of in-stent restenosis after BMS is late loss due to in-stent neointimal formation, whereas both elastic recoil and negative remodelling are virtually eliminated by stent scaffolding.[1] DES have recently revolutionized interventional cardiology, since they have demonstrated to reduce both BAR and the need for subsequent revascularization procedures[2-20] without increasing the risk of stent thrombosis, at least during the first year and under prolonged double antiplatelet therapy,[31] although the possible effect of DES over the risk of very late (>1 year) stent thrombosis is still to be quantified.

ISLL as a surrogate of DES effectiveness

BAR (presence of stenosis severity > 50% at 6-9 month follow-up) has been the most commonly used angiographic parameter in order to compare different devices in interventional cardiology. However, continuous measurements, such as MLD, percent diameter of stenosis, and late loss, have the advantage of being able to quantify more precisely the long-term angiographic benefit of a therapeutic mean, thus necessitating less patients to demonstrate the efficacy of a given device. As it is very intuitive, appealing from a mechanistic point of view, and not referred to RVD, ISLL has been used in many DES trials. ISLL reflects the biological effect (inhibition of neointimal formation) of DES in a very precise way, and because of that it is now being used as a surrogate endpoint in some randomized trials that are comparing different types of DES.

However, despite these considerations, many authors believe that the clinical implications of ISLL are limited, taking into account some recent findings from some randomized trials. First, data from the TAXUS-IV study have suggested that only when ISLL exceeds 0.5 mm there is an increase in the need for TLR, whereas mean ISLL lower than 0.5 is associated with extremely low rates of TLR, arguing also that coronary stents may accommodate an up to 0.5 mm ISLL inside the stent without increasing the need for new revascularizations.[22] Second, different types of DES have been associated with different ISLL values (0.17, 0.39, and 0.62 mm in the SIRIUS, TAXUS-IV, and ENDEAVOR-II trials, respectively), but rather similar rates of TLR (4.0, 3.0, and 4.6%, respectively).[3,14,17] Finally, some recent trials comparing different types of DES have shown some discrepancies between angiographic and clinical data. For example, in the recently reported ENDEAVOR-III trial, where ZES and SES were randomly compared, mean ISLL was much lower in patients allocated to SES (0.15 vs. 0.60 mm), but

the rates of target vessel revascularization were not significantly different (5.3 vs. 6.0%, respectively).[30]

Our results show that mean ISLL is associated with the degree of clinical benefit of using DES instead of BMS, quantified as the NNT for TLR. NNT is probably the best parameter for measuring the clinical impact of a given therapy. Lower mean ISLL was associated with lower NNT for TLR. An important finding of our study was that the clinical implications of mean ISLL are present even within the range of mean ISLL lower than 0.5 mm (most trials included had a mean ISLL lower than 0.5 mm in patients allocated to DES).

Because BAR rates after DES implantation are lower than that for BMS, and low binary event rates result in decreased statistical power in randomized trials, the number of patients needed to make comparisons between new and proven DES has increased substantially. As ISLL is a continuous endpoint, it allows to compare the efficacy of different types of DES without the necessity of using extremely large populations of patients. In a recent study, Mauri *et al.*[32] have demonstrated that ISLL is strongly correlated with the rates of both BAR and TLR when using DES. In the present study, we have extended this relationship to the degree of clinical benefit of using DES instead of BMS (NNT for TLR). Moreover, by using ΔISLL, we have adjusted mean ISLL in patients allocated to DES by the angiographic behaviour of the respective BMS, thus demonstrating that the degree of inhibition of neointimal formation after stenting by the use of DES is strongly associated with the clinical impact of using DES instead of BMS.

Comparison among different types of DES

This meta-regression analysis evaluated the relationship between angiographic behaviour of DES and the clinical benefit of using DES instead of BMS, but not the comparison between different types of DES. Our present study therefore does not allow to obtain conclusions about comparison of different types of DES. However, our findings suggest that among all the different types of DES evaluated in the trials included, the SES shows the most evident angiographic and clinical benefit when used instead of BMS. Studies that compared BMS with the SES showed the lowest NNT for BAR and also for TRL. Considering the NNT for TLR as the measurement of the clinical benefit of using DES instead of BMS, this benefit was progressively reduced in SES, PES, EES, ZES, and TES (mean NNT for TLR 6.8, 11.9, 11.1, 13.3, and 20.4, respectively) (*Figure 3*).

SES and PES are the most widely used DES, due to their proven efficacy in reducing TLR in comparison with BMS in a large number of randomized trials.[2–16] Several randomized trials have compared these two types of DES, with discordant results.[23–28,33] Although angiographic follow-up was more favourable with SES in most cases, clinical differences were obtained only in some of them. A possible reason for these discordant results may be the inclusion of higher risk patients in some trials such as ISAR-DESIRE and ISAR-DIABETES, in comparison with others such as the REALITY study. We have recently performed a meta-analysis from the TAXI, REALITY, ISAR-DESIRE, ISAR-DIABETES, and SIRTAX trials.[34] We found that TLR was significantly lower in patients allocated to SES in comparison with PES (5.0 vs. 7.4%, $P < 0.01$), and the same occurred with target vessel revascularization (6.1 vs. 8.3%, $P = 0.02$) and BAR (9.0 vs. 12.4%, $P = 0.002$), whereas the risk of stent thrombosis was similar. Consistent results have been recently reported by Kastrati *et al.*,[35] in which the CORPAL trial was also included. The superiority of the SES in reducing the rate of BAR and TLR is probably explained to the higher reduction of ISLL. Several factors may be related with this different angiographic behaviour after SES or PES. First, sirolimus and paclitaxel have different mechanism of action (whereas sirolimus is cytostatic, paclitaxel is cytotoxic). Second, both types of DES have different drug-release kinetics (the polymer coating of SES allows the elution of nearly 100% of the drug within 1 month, whereas in the case of PES the polymer allows the eluting of only 10% of the drug over 2 months, with 90% of paclitaxel remaining sequestered in the polymer indefinitely). Finally, both stents have different designs: a closed-cell design in the case of SES, and an open-cell design in the case of PES.[35]

Head-to-head trials comparing newer DES with either Cypher or Taxus are still scarce. The ENDEAVOR-III trial has not shown statistically significant differences between patients allocated to ZES or SES in terms of TLR. However, owing to the study design (3:1 randomization), the number of patients allocated to PES was low.[30] In the ISAR-TEST trial, a non-polymer on-site coating with rapamycin (Yukon stent) was not inferior to PES in 450 patients. Other head-to-head randomized trials, such as SPIRIT-II (Xience V [Guidant Corp.] vs. Taxus), ZOMMAX I (zotarolimus-eluting Zommax stent [Abbott] vs. Taxus), or NOBORI I (biolimus-eluting Nobori stent [Terumo] vs. Taxus) are currently ongoing.

Study limitations

First, the present study has the inherent limitations of meta-regression techniques, such as the possibility of having missed some confounder variables.[36] Second, ISLL may vary among different stent platforms, and thus the use of different BMS in the trials included may have influenced the results. However, in order to prevent any bias related with differences among different types of BMS, we also used ΔISLL as a measurement of the angiographic benefit of DES. Third, ISLL may also vary among different core laboratories, but this limitation was also overcome by the use of ΔISLL, since angiographic data from patients included both in DES and BMS groups were measured in the same core laboratory in each trial. Fourth, ISLL may vary with some patient and lesion characteristics, such as the presence of diabetes, RVD, or lesion length. The results of the meta-regression analysis, however, were maintained after adjusting for these variables. Finally, routine angiographic follow-up may influence the rate of TLR, and it could be speculated that the NNT for TLR might be higher in all trials in case the routine angiographic follow-up was not performed.

Conflict of interest: none declared.

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Clinical vignette

doi:10.1093/eurheartj/ehl513
Online publish-ahead-of-print 9 February 2007

Isolated left ventricular diverticulum in an asymptomatic patient

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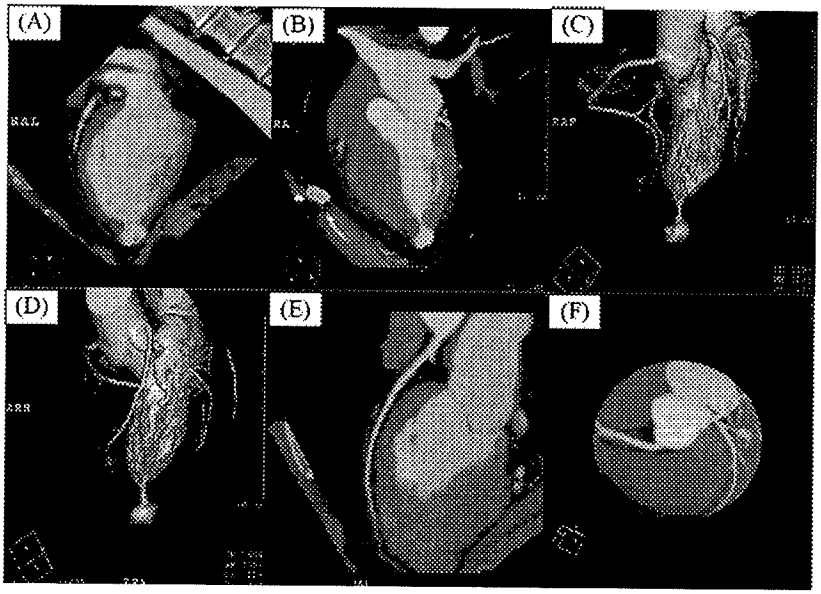
A 47-year-old male with intermediate risk of coronary artery disease and atypical chest pain was referred to our hospital for multislice computed tomography (MSCT) coronary angiography. MSCT of the patient revealed apical interruption of myocardium and apical diverticulum (15 × 11 mm) of the left ventricle (Panels A–F). The ECG of the patient was normal sinus rhythm, and the patient had no history of myocardial infarction.



Congenital diverticulum of the left ventricle is a rare cardiac malformation that frequently includes other congenital defects involving the abdominal wall, sternum, diaphragm, pericardium, and heart. Isolated left ventricular diverticulum is found in 30% of cases and is associated with numerous serious complications, such as cardiac arrhythmias, sudden death, endocarditis, systemic emboli, heart failure, cardiac rupture, and intraventricular obstruction. Surgical resection is the treatment of choice in symptomatic patients, whereas the management of asymptomatic patients often represents a therapeutic dilemma.

Panels A and B. Two-chamber MSCT views of left ventricle during diastole (Panel A) and systole (Panel B) demonstrating apical interruption of myocardium and apical diverticulum (15 × 11 mm) with nodular calcifications on the thinned wall.

Panels C and D. Post-processed three-dimensional rendered systolic images of left ventricle after extraction of myocardium demonstrating apical diverticulum resembling a tear drop falling from the heart.

Panels E and F. MSCT coronary angiography of the patient demonstrating normal coronary arteries (Panel E, left anterior descending artery; Panel F, proximal sections of coronary arteries).

See online Supplementary material for a colour version of this figure available at *European Heart Journal* online.

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GICS SECTOR	HEALTH CARE
US Strategist Weight	14.8%
S&P 500 Weight	12.8%

Industry Overview

February 24, 2005

Notes from our 2005 Interventional Cardiology Conference

- **ACC could be an inflection point for J&J's Cypher DES program**
  At the end of 2004, there were some smaller trials suggesting that Cypher has superior **efficacy** compared to Boston Scientific's TAXUS. This could be further reinforced by the results of the full clinical data set for the Cordoba/Las Palmas, REALITY and SIRTAX trials. If the comparative **safety** profile also trends in a similar direction, Boston Scientific could be dealt a knock-out blow.
- **Longer-term excitement of non-stainless steel stent platforms**
  Clinicians were upbeat about the prospects for Conor Medsystems' COSTAR program, Guidant's SPIRIT program and Abbott's ZoMaxx program. With respect to Medtronic, little new was uncovered. Most agreed that this product should probably play a niche role. This assumes that ENDEAVOR II late loss remains high.
- **Reimbursement problematic for carotids, but AAA should take off**
  Due to a restrictive reimbursement environment, our expectations regarding carotid stenting may prove optimistic. On the flipside, growth in the AAA stent graft market could accelerate, especially if the SAAAVE bill is approved by Congress.
- **Need to wait until the end of the decade for the next big thing**
  Areas of excitement include (1) a stent-like ICD that can be implanted by interventional cardiologists, (2) percutaneous valve repair/replacement, (3) nano sensors to monitor the performance of implanted devices, and (4) new CHF stimulation devices that are not currently addressed with existing ICD-CRT therapy.
- **Maintaining Ratings on Stocks**
  We are maintaining our Equal-weight ratings on BSX and STJ and Overweight ratings on MDT and ABT. As for GDT and JNJ, these two names are unrated. In the case of MDT and ABT, we think expectations are low regarding these two companies' prospects in the interventional cardiology market.
- **Industry view: Attractive**
  Fundamentals remain strong, and growth prospects look relatively robust for stocks in our coverage universe. With limited growth opportunities in the equity market and an increasingly uncertain outlook for large cap pharmaceuticals stocks, we view the med tech space as a reasonable place for investors to find growth.

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Notes from our 2005 Interventional Cardiology Conference

Morgan Stanley & Co. Incorporated ("Morgan Stanley") is currently acting as financial advisor to Guidant Corporation ("Guidant") with respect to its announced proposed acquisition by Johnson & Johnson ("Johnson & Johnson").

The proposed transaction is subject to, among other things, the consent of Guidant shareholders. This report and the information provided herein is not intended to (i) provide voting advice, (ii) serve as an endorsement of the proposed transaction, or (iii) result in the procurement, withholding or revocation of a proxy or any other action by a security holder.

Please refer to the notes at the end of this report.

Summary and Investment Conclusion

On February 24, 2005, we hosted our eighth annual half-day conference on interventional cardiology. As we pointed out in our recently published Investors' Guide to Interventional Cardiology, the market for the drug eluting stents (DES) is maturing. This in turn is leading to a slowdown in the $8.75 billion interventional cardiology market. For this reason, the focus of the conference was on two topics: (1) the competitive dynamics of the DES market and (2) future growth opportunities in the interventional cardiology market that are not DES based. Below are some of the thoughts from our conference.

ACC: A possible inflection point for J&J (Cypher)

Clinicians on the interventional cardiology panel appeared very excited about the upcoming American College of Cardiology (ACC). While not explicitly stated, it appears that this meeting could prove to be an inflection point for J&J. Specifically, at the end of 2004, there were some smaller trials (ISAR DESIRE and partial data for Cordoba/Las Palmas) that suggested the efficacy of Cypher in more complicated lesions may be superior to Boston Scientific's TAXUS drug eluting stent. This could be further reinforced by the results of the full clinical data set for Cordoba/Las Palmas, REALITY and SIRTAX. As such, Boston Scientific could be at risk.

Even more important to physicians will be the comparative safety of these devices. We expect some concerns over safety to be raised from the TAXUS V trial. If in fact the comparative safety profile in REALITY and SIRTAX are also trending in Cypher's favor, Boston Scientific could be dealt a knock-out blow. Stay Tuned.

Excitement over SPIRIT, COSTAR and ZoMaxx

With respect to new stent platforms, this group of clinicians were certainly upbeat about the prospects for new stent DES platforms, including Conor Medsystems' COSTAR, Guidant's SPIRIT program and Abbott's ZoMaxx program. With respect to Guidant and its development timelines, we heard some good news and bad news. First, the bad news -- the company's U.S. pivotal trial, SPIRIT III will probably not start before the end of the first quarter. That said, beginning of enrollment should be soon thereafter. On a more positive note, this trial will also be used to gain Japanese regulatory approval. As such, we think this confirms our aggressive assumption for a 2007 Japanese launch.

With respect to Medtronic, minimal new information was uncovered at the conference. This group of clinicians certainly believes that late loss is important. For this reason, they believe that if late loss proved to be high in the ENDEAVOR II, the product would serve a "niche" role as it deliverability is superior. This is pretty consistent with our expectations. That said, given the low expectations for this trial, we think there may be room for some upside surprise. **Finally, despite comments made by some of our competitors, ENDEAVOR II data will be complete with normal number of patients returning for follow up.**

Another major focus of our conference was in the area of non-coronary procedures. These include the repair of abdominal aortic aneurysms (AAA) and carotid artery stenting (CAS).

AAA Market: Poised to accelerate

The abdominal aortic aneurysm (AAA) stent graft market has grown to $330 million in 2004. We think this market could grow in the low double-digits, while Dr. Ohki may be more optimistic. The bad news is that Medtronic is losing share in this market to new upstarts, such as privately held W.L. Gore and Cook. The good news is that the market will reaccelerate with the anticipated passing of the

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SAAAVE (Screen Abdominal Aortic Aneurysms Very Efficiently) bill in Congress. This bill will provide funding of AAA screening for patients deemed to be at high risk (for example, elderly patients who smoke) for AAA. Additionally, FDA approval for endografts to treat thoracic aneurysms is also anticipated to enhance market growth.

Carotids: Medicare funding is problematic

Regarding carotid stents, we expect that the market is about to "take off" with the recently gained FDA approval for the first carotid stent system (Guidant's Acculink w/ Accunet). Unfortunately, our panel agreed that we might be too optimistic as CMS (Centers for Medicare and Medicaid Services) has limited reimbursement to severely symptomatic patients. We expect the competitive dynamics will only become more intense from here on out as Boston Scientific and JNJ are expected to gain FDA approval in 2Q05. Both Abbott and Medtronic expect to gain FDA approval later in the year. Finally, ev3 expects to gain FDA approval for its carotid stent in 2006.

In 2004, we estimate the worldwide carotid market was around $60 million. By 2008, we expect this market to reach the $580-$600 million range. This assumes that CMS will be more forgiving with respect to reimbursement.

The next big thing: we need to wait!

We also had a peek into the future from Dr. Marty Leon from Columbia University. His task was to present new technologies that are expected to impact this market in the future. The good news is that there are many exciting unmet medical needs that can be addressed with device therapy. The bad news is that none of these technologies will likely be material until 2009, at the earliest. As such, the near-term future of the interventional cardiology market will depend on drug eluting stents. Among the most exciting new technologies that were presented by Dr. Leon were: (1) downsized, stent-like ICDs (Interventional Rhythm Management)delivered by interventional cardiologists 2) percutaneous valve repair (Edwards and Viacor), 3) nano sensor technology (Remon Medical and CardioMEMS) and 4) new stimulation devices to treat heart failure (Impulse Dynamics).

Price Targets, Ratings and Risks

Abbott Laboratories (ABT, $46, Overweight). We maintain our Overweight rating on ABT shares. Our price target for ABT is $52, and is based on a 1.10–1.15 relative multiple to the S&P 500 on estimated 2006 earnings. We think that our relative multiple target is justified, considering Abbott's projected 11% long-term growth rate and 2.4% yield. These numbers compare with a projected normalized S&P 500 growth rate of 8% and a 1.6% yield.

Overall, we remain confident in Abbott's ability to increase earnings at an above-average rate (compared with other pharma companies). We also think that its pipeline, which includes 1) Humira for psoriasis and Crohn's disease, 2) Oral Zemplar for pre dialysis patients, 3) Simdax for heart failure, 4) Xinlay for prostate cancer, and 5) ABT 874 for Crohn's, is among the most robust in the pharmaceutical industry. As such, we are maintaining our Overweight rating on ABT. We think that as investors feel more comfort with the risks the company is facing regarding the financial impact of Synthroid, Tricor and Biaxin, the stock's multiple will continue to improve and investors should focus more on the company's pipeline.

We see a number of risks to ABT's reaching our price target. The first relates to political risks facing the pharmaceutical industry. Any major macro changes that affect pricing will definitely impact Abbott and its prospects, we believe. Abbott's TAP Pharmaceutical joint venture is one of these. Specifically, the generic approval for OTC Prilosec has caused growth of TAP's Prevacid to slow. We think that we have adequately captured this in our estimates. TAP is an important contributor to Abbott's earnings. Other risks to earnings, in our view, include the timing for generic competition Tricor and Biaxin. Finally, we see the company's FDA approval strategy for Xinlay as fairly risky. It is possible that approval could be delayed or denied. We do, however, see other earnings levers that could potentially make up for lost Xinlay sales.

Boston Scientific (BSX, $33, Equal-weight). Despite what appears to be an attractive valuation, we are maintaining our Equal-weight rating on Boston Scientific. We still see Boston Scientifics' DES franchise coming under competitive pressure in future years. The extent of that pressure might be clarified at the upcoming American College of Cardiology meeting. We think that at that meeting, enthusiasm for JNJ's Cypher will be renewed with the release of several trials that will be suggestive of superior efficacy for Cypher over BSX's TAXUS. Boston Scientific might come under further attack if the fears over the safety data for TAXUS V materialize as well. Longer term, we still think that Abbott, Medtronic and the Guidant

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(as either a standalone or part of JNJ) will all be formidable competitors. As such, we find it hard to make a case for the stock to appreciate in the coming months.

Guidant (GDT, $73, NR). *Due to the announcement of the J&J/GDT transaction, we currently do not have a rating or price target on Guidant.*

Johnson & Johnson (JNJ, $66, NR). *Due to the announcement of the J&J/GDT transaction, we currently do not have a rating or price target on J&J.*

Medtronic (MDT, $53, Overweight). Our price target of $60 is based on a 1.55-1.60 relative multiple to the S&P 500 on our projected calendar 2006 earnings. This price target is a premium to the nine-year average relative multiple of the stock of 1.43. Given the condition of the market today in which the market is "growth starved", we suspect that the market will pay premiums for companies with substantial organic growth. While our $60 price target is a premium to the stock's historical **relative** multiple, a 25x multiple on forward calendar earnings is actually a two-to three multiple point discount to its **absolute** historical multiple. Hence, we think that this target is reasonable.

We estimate the company's projected total return (defined as earnings growth and dividend yield) to be 15.6%, versus 9.6% for the S&P 500.

There are risks to our price target and earnings projections. Our revised estimates assume that Medtronic achieves a 12% DES market share position in Europe in calendar 2005 and 15%+ share in calendar 2008. If the ENDEAVOR stent is seen as significantly less competitive to Cypher and TAXUS, this share position could be considerably lower in dollar terms. Other risks include possible share loss and slower market growth for ICDs. We also continue to project healthy growth for the company's spinal business. If we begin to see rapid uptake for competitive artificial discs, this could put pressure on the company's traditional spinal fusion franchise.

Industry View: Attractive

Fundamentals remain strong, and growth prospects look relatively robust for stocks in our coverage universe. With limited growth opportunities in the equity market and an increasingly uncertain outlook for large cap pharmaceuticals stocks, we view the med tech space as a reasonable place for investors to find growth.

Details

A Glimpse of the Future: Marty's Top Ten List

Dr. Martin Leon, Director of the Center for Interventional Vascular Therapy at Columbia University Medical Center in New York City, gave an overview of how far we have come in the evolution of interventional cardiology and an outlook on "what's next" in this dynamic market.

To date, the drug eluting stent (DES) has been the most significant innovation in the interventional cardiology market. Over the past 25 years, therapy has evolved from plain balloon angioplasty to new device angioplasty (such as atherectomy) to the "stent frenzy" of the mid 1990s and ultimately to the commercialization of the Cypher DES in 2003.

Nevertheless, there remain areas that need further investigation, including: (1) more safety data in "real world" scenarios, 2) more long-term durability data, and (3) more efficacy data in specific lesions subsets, such as left main disease, bifurcations, peripheral vascular disease, and acute MIs. Data regarding these issues is expected over the next several years with much of the recent clinical focus on comparable safety and efficacy data among market participants. In addition, Dr. Leon cited the immediate need for an optimized workhorse stent (particularly as it relates to deliverability), the need for physician training as well as additional clinical trials in complex lesions, and PCI enhancements.

As DES penetration approaches the 85-90% range in the United States, however, the focus in interventional cardiology will begin to shift to developing new technologies to treat the vast array of current unmet needs. While there are a plethora of emerging technologies in early stage development to address these needs, there are no short term "home runs" and most of the opportunity lies in the 2009-2010 time frame. As such, there is probably little that will prevent the interventional cardiology market from slowing over the next three to four years.

Dr. Leon addressed ten emerging technologies and factors that will help drive growth in the interventional cardiology market over the next several years.

1. **Acute Myocardial Infarction (AMI) - Vulnerable plaque: Way too early.** Only one third of heart attacks are due to the narrowing of arteries. The greater issue is "vulnerable plaque", which can burst and set off a

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series of potentially lethal events. It is believed that inflammatory pathways have something to do with the formation of vulnerable plaque. That said, we are a long way from finding efficient detection and proving that device therapy will be effective. There are at least four technologies being developed in this area that show promise of potential commercialization: (1) intravascular ultrasound, (2) virtual histology, (3) palpography, and (4) thermography. This opportunity will likely take 5-10 years to develop.

2. **Acute Myocardial Infarction Therapies: A series of disappointments.** Marty pointed that that companies will likely focus on techniques to improve myocardial viability during and after myocardial infarction. To date, device therapy has been met with dismal failure as hypothermia, distal protection devices, aqueous oxygen and thrombectomy have not proven to be effective.

3. **Enhanced Diagnostic Imaging: Great advances seen already.** Dr. Leon has been awed by recent improvements in imaging technology. CT angiography, MR Imaging, guided intravascular ultrasound have led to dramatic improvements. Unfortunately, for healthcare investors, there are few "pure plays" in this arena. This might however, lead to more patients screened for possible DES implantation.

4. **Endovascular Therapy: Still in its infancy.** Overall, endovascular therapy has been gaining acceptance in the physician community. The primary endovascular targets include: (1) carotid stenting, (2) renal stenting, (3) AAA endografts, (4) thoracic endografts, and (5) venous disease. Among these therapies, carotid stenting and AAA have been the most widely accepted to date. Going forward, we believe that the endovascular market should continue to represent a significant opportunity. That said, our panelists were relatively cautious about the prospects for peripheral drug eluting stents. (As a side note, panelists at our conference were a bit awed with the "hype" surrounding FoxHollow's Silverhawk atherectomy device. Most view this product as a niche product, at best).

5. **Structural Heart Disease: Big potential, but some time away.** Dr. Leon was generally enthusiastic about the opportunities in percutaneous mitral valve repair and aortic valve replacement. Of the two, repair will probably materialize sooner. Currently, there are several companies vying at this opportunity, including Viacor, Edwards Lifesciences, and CoreValve.

6. **Interventional Congestive Heart Failure (CHF): Some really interesting disruptive technologies.** Perhaps one of the most significant opportunities going forward, in our view, is the potential for interventional devices in the treatment of CHF. Dr. Leon views bi-ventricular pacing devices and implantable cardioverter defibrillators as the "tip of the iceberg" when it comes to treating congestive heart failure. Two potential device CHF therapies that appear to have significant market potential are: (1) Cardiac Contractility Modulation (Impulse Dynamics) which is an electrical stimulation device used to relieve symptoms of CHF and (2) an Interventional Intravascular Defibrillator (IID being developed by Interventional Rhythm Management). IID is a downsized defibrillator that can be implanted in 10 minutes by an interventional cardiologist.

7. **Micro and nano-technology** is another area that we believe will represent a strong opportunity down the road. In particular, we believe there is a high probability of nano-technology being an effective tool for patients to monitor AAAs stent grafts. Remon Medical and CardioMEMS are the leaders in this emerging market as it had a small sensor that can be implanted to monitor cardiac function.

8. **Refractory Ischemia: Very disappointing to date.** Over the past decade, there have been many attempts to grow and create new vessels to relieve ischemia with little success. It sounds like this opportunity will develop later, rather than sooner.

9. **Adjunctive PharmacoRx: A must.** Pharmaceutical therapy within interventional cardiology has been strong beneficiary of the drug eluting stent boom. In particular, all patients who receive a DES take anti-platelet drugs such as Plavix and Aspirin following the procedure. Potential opportunities down the road for interventional pharmaceutical products relate to anti-thrombins, PCI reperfusion strategies, and precise glycemic control in diabetes. Overall, it is important to note that pharmaceutical and device therapies **are not** competitors but rather complimentary to one another.

10. **Physician Training: Also a must.** Lastly, Dr. Leon noted physician training as a potential barrier to growth

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in the interventional cardiology market. We would expect some more technology-based training methodologies to be introduced over time. Overall, the educational process will need to evolve, as new technologies and therapies come to market.

Among these technologies, we are most encouraged about the commercial opportunities for 1) the downsized, stent-like ICDs (IID, Interventional Rhythm Management), (2) Percutaneous valve repair/replacement (Edwards and Viacor), 3) Nano sensor technology (Remon Medical and CardioMEMS) and (4) New stimulation devices to treat heart failure (CCM by Impulse Dynamics). As mentioned above, however, many of these technologies are several years away.

Update on AAA Stents and Carotid Stenting

Next, Dr. Takao Ohki, Chief of Vascular and Endovascular Surgery at the Montefiore Medical Center in New York, presented information on the current, less invasive approaches to treating abdominal aortic aneurysms (AAA) and carotid artery stenting.

AAA Market: Poised to Accelerate

Dr. Ohki began his presentation on a discussion on the AAA market. In general, Dr. Ohki remains excited about the long-term prospects of this market, estimated to be around $330 million in 2004. We think this market could grow in the low double-digits, while Dr. Ohki may be more optimistic. Below is a summary of the key points highlighted on AAA market by Dr. Ohki:

- **Recent clinical data continues to support benefits of AAA stent grafts.** Dr. Ohki pointed to data presented in 2004 from (1) a randomized prospective study called EVAR 1 and (2) the DREAM trial (Dutch). Both demonstrated a dramatic reduction in 30-day mortality, hospital stay and length of operation.

- **Increasing public awareness of AAA also a boost:** Dr. Ohki also believes that increasing public awareness of AAA stent grafts should help support penetration of this device in the future. Dr. Ohki pointed out that approximately 200,000 patients are diagnosed with AAA annually in the U.S., even with little screening. With the advent of newer imaging technologies such as ultrasound and CT (computed tomography) imaging, AAA stent graft penetration should accelerate.

- **Positive signs on reimbursement, although more will be needed:** As for reimbursement, the anticipated passing of the SAAAVE bill in Congress should also provide tailwind for reacceleration in this market. This bill will provide CMS funding of AAA screening for patients deemed to be at high risk (for example elderly smokers) for AAA.

In terms of the competitive landscape in the U.S., Dr. Ohki indicated that Medtronic's AneuRx stent graft continues to the market leader, although share has been declining due to concerns over efficacy and deliverability (migration of stent). Medtronic is working on enhancements to address these issue with the AneuRx II. Overseas, Medtronic's Talent stent graft is the leader in Europe, although the company will most likely need to initiate a new clinical trial to obtain FDA approval.

In terms of share gainers in this market, Dr. Ohki highlighted the Cook Zenith and the WL Gore Excluder devices as growing in market acceptance. In part, he attributed the momentum of Cook to the company's focus on offering a variety of devices to cover the entire aortic disease. We estimate that Cook and WL Gore are the #2 and #3 players currently on the market. Endologix recently gained FDA approval for its PowerLink device, but Dr. Ohki was not optimistic about this graft given concerns over versatility and stent migration. Other competitors trying to gain a footprint in this area include J&J (Fortron, US/OUS launch 1Q07/3Q06) and Boston Scientific (Trivascular, US launch 4Q07).

On a related note, Dr. Ohki highlighted thoracic aneurysms as an opportunity which may enhance growth for the endograft market. The FDA approval (with conditions) of the Gore TAG thoracic endoprosthesis is a positive step in expansion into this segment, which Dr. Ohki estimates to approximate 22,000 procedures, representing a $220-250 million opportunity. Medtronic and Cook are also looking to enter this market. Medtronic could be on the market as early as late 2005.

Carotid Stenting: Medicare Funding is Problematic

On the carotid artery stenting (CAS) front, Dr. Ohki indicated that excitement continues to surround this therapy.

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For perspective, we estimate this market to be around $150 million worldwide in 2005, growing to $600 million in 2008. Dr. Ohki thought that this estimate might prove to be a bit optimistic.

- **Limited reimbursement remains key concern:** Despite growing enthusiasm, CMS remains a key concern. In particular, in December 2004 CMS's draft decision limited CAS reimbursement only for high risk patients with > 70% stenosis (in combination with other symptoms such as Class III/IV heart failure, ejection fraction < 30%, unstable angina). This means that any asymptomatic or symptomatic patients with stenosis of 50-69% (part of FDA approval) will **not** be covered, reducing market potential at least in the near term. CMS plans to announce its final decision on March 17, 2005. Many stakeholders (including Guidant, the first manufacturer to have FDA approved carotid system) have already raised objections to this decision. Dr. Ohki does not expect CMS to change its draft decision and suspects that further data will be needed on asymptomatic patients for these guidelines to change.

- **Optimism for CREST and ACT I:** Speaking of the expanding patient population, Dr. Ohki did express optimism regarding the CREST study (NINDS, NIH) and the ACT I trial (Abbott Labs), both of which include asymptomatic patients (see our note dated February 23, 3005 -- *2005 Investors' Guide to Interventional Cardiology).* However, we do not expect meaningful data on this patient segment to be available in the near term. As such, we expect the uptake of this market to be more pronounced in 2007, partly due to the potential expansion of indication to this patient group.

- **Off-Label Use a "No-No":** Dr. Ohki was adamant that off-label use of CAS will be very limited, especially given CMS' hawkish attitude on the monitoring of this issue. Additionally, most physicians remain concerned and sensitive regarding off-label usage given the complexities of the procedure.

Dr. Ohki reminded investors that other issues to watch for in this market include the "turf war" between interventionalists and vascular surgeons, as well as the steep learning curve and certification process associated with carotid stenting. We suspect that this turf battle may have been behind the CMS decision mentioned above.

With respect to the competitive landscape in carotids, Guidant remains the only manufacturer with an FDA approved system in the U.S (3Q04 approval). Dr. Ohki indicated that the availability of Rapid Exchange (Rx) technology remains a key differentiator, which may favor Guidant and Boston Scientific. We expect the competitive dynamics will only become more intense from here on out as Boston Scientific and JNJ are expected to gain FDA approval in 2Q05. Both Abbott and Medtronic expect to gain FDA approval later in the year. Finally, ev3 expects to gain FDA approval for its carotid stent in 2006.

From Benchtop to Reality: Issues that remain in the DES market

Dr. Elazer Edelman, Director of the Harvard-MIT Biomedical Engineering Center in Boston was our next presenter. As an M.D. who focuses on biomedical engineering, Dr. Edelman was asked to speak to our group and discuss current scientific issues that the FDA is still grappling with regarding the drug eluting stent market. He focused on three major issues that are on the minds of the FDA:

1) Material/ Stent Interface: As drug eluting stents are sterilized and expanded, the polymer coatings on the stents tend to flake off and crack. Additionally, for the most part, quality control remains an industry wide problem. For this reason, he is excited about future DES programs that do not require polymers.

2) Drugs: Contrary to popular belief, there is no dose response for DES drugs in terms of efficacy. He is more concerned about the rate of release and the impact of having excess drug inside the stent for extended periods. We suspect that he was hinting of his concern that the vast majority of drug on a TAXUS stent remains present even several months after insertion.

3) There is no correlation between *in vitro* and *in vivo* results: Dr. Edelman thinks that this probably has to do with the solubility and molecular weight of the drugs. The environment and type of vessel might also play a role since these drugs bind to different proteins. For example, how else can one explain why drug eluting stents work well in

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the coronaries but not in the periphery? Change in elastin levels in the artery might explain the differences in efficacy.

Overall, Dr. Edelman thinks that there are differences in current DES approved drugs and the way they bind to the vessel. This may explain why Cypher might end up performing better than TAXUS in several difficult lesion subsets, such as in stent restenotic lesions. It may also explain why the use of multiple overlapping stents might cause thrombus. Here too, we feel that he was hinting that Cypher may be preferred in this situation as well.

DES: Update and Emerging Platforms

The final presentation of the day came from Dr. Campbell Rogers, Director of Cardiac Catheterization Lab at the Brigham & Women's Hospital. Dr. Rogers' focus was on the current battle within the DES market as well as a review of new stent entrants.

Late Loss Matters:

Dr. Rogers started off the presentation talking about statistics and his biases regarding data presented to date. For example, he is a big believer that late loss is important, and the lower the late loss, the better. This perhaps explains why clinicians in his practice have been loyal Cypher users since the product's launch. In his lab, 80% of drug eluting stents that are currently implanted are Cypher DES. This compares to 25% Cypher share for interventional cardiology physicians who work in his lab but are not part of his practice. He is generally less concerned about ease of delivery (which favors TAXUS), and more concerned about comparative safety and efficacy.

Next, Dr. Rogers talked about the data presented to date from various trials, and a pattern of performance suggesting that in more complicated vessels, Cypher tends to win out compared to TAXUS. The results from (1) "Long DES" trial (2) preliminary data from a Spanish trial (Cordoba/Las Palmas), and (3) ISAR DESIRE all reinforced this opinion.

ACC will be critical for Boston Scientific:

Perhaps more important to Dr. Rogers is the issue of safety with respect to drug eluting stents. Here too, Dr. Rogers was suggestive that Cypher might prove to be safer. As such, this year's ACC will be critical for both J&J and Boston Scientific. Specifically, full results of several head-to-head Cypher/TAXUS trials including REALITY, Cordoba/Las Palmas and SIRTAX will all be presented at the ACC. Additionally, TAXUS V, which looks at the use of TAXUS (vs. bare metal stents) in complicated lesions, will be presented.

As we have written about before, we think that TAXUS V has some safety issues pertaining to the use of overlapping stents. Taken by itself, the panel thought that this issue may not be a big deal. However, if the other head-to-head trials also suggest differences in safety, it could be a knock-out blow for Boston Scientific!

Specifically, as of today, we expect that consensus expectations are that these head-to-head trials will demonstrate (with statistical significance) lower late loss for Cypher when compared to TAXUS. On the other hand, this is not expected to manifest itself in differences in clinical restenosis or safety, since these trials are generally underpowered to show such differences. Therefore, it was the opinion of our panelists that if statistically significant differences in safety are detected, the current market dynamics could shift dramatically in favor of J&J since "one ounce of safety is worth more than a pound of efficacy". As such, even a consistent (non-statistically significant) trend of safety data suggesting that Cypher is safer than TAXUS might also accomplish the same thing. In our view, the body language from our panelists was clearly not good for Boston Scientific. Stay Tuned.

What about newer stent platforms?

Regarding newer stent platforms, Dr. Rogers' commentary were as follows. First, he agrees with our thesis that cobalt chromium stents will eventually dominate the DES market. Although clinicians had not used Boston Scientific's next generation stainless steel Liberte stent, most of our panelists found it hard to believe that it would be preferred over cobalt chromium. Second, with respect to Medtronic's ENDAVOR program, Dr. Rogers thinks that this is a "niche" product, if the high late loss witnessed for ENDEAVOR I is also seen in ENDEAVOR II. He also thinks that the product will be used mainly in cases where Cypher and TAXUS stents cannot be delivered properly to a vessel. This confirms our view that Medtronic's cobalt chromium platform will prove superior in terms of deliverability but inferior to Cypher and TAXUS in terms of efficacy. **Finally, during our panel discussions, we did have some specific discussions of the ENDEAVOR II trial. Despite comments made by some of our competitors, ENDEAVOR II data will be complete with normal number of patients returning for follow up.**

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Regarding Guidant's SPIRIT program, optimism is high given the strong SPIRIT First results. On a slightly negative note, the first investigators meeting for SPIRIT III will probably not take place until the middle of March. This probably pushes back the start of this trial from late Q1 to Q2. On the other hand, results from SPIRIT III will also be used for Japanese approval. As such, we think this confirms our aggressive assumption for a 2007 Japanese launch. Dr. Rogers did think that if the J&J/Guidant deal closes, J&J would elect to drop its chromium cobalt stent program (Cypher Neo) and favor another one that uses Guidant's Vision stent.

In terms of other programs, Dr. Rogers is also optimistic about Abbott's ZoMaxx program and Conor Medsystems' COSTAR program. Down the road, he was intrigued with fully bioabsorbable stents. Stay Tuned.

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Exhibit 1

Worldwide Sales by Manufacturer, 2001-2008E

Boston Scientific

($ millions)	2001	2002A	2003A	2004E	2005E	2006E	2007E	2008E
	$1,319	**$1,401**	**$1,756**	**$3,625**	**$4,122**	**$4,182**	**$3,592**	**$3,538**
Coronary Stents	344	318	527	2,351	2,775	2,683	1,942	1,721
Conventional Angioplasty	$593	$609	$692	$752	$793	$826	$860	$895
Peripheral Stents	141	152	166	172	184	193	204	215
Carotid Stents	0	2	5	5	17	45	80	130
Embolic Protection	2	13	32	51	65	95	125	155
Atherectomy	170	224	200	137	106	93	89	84
Intravascular Ultrasound	69	84	134	157	172	182	192	203
Vascular Closure	0	0	0	0	10	65	100	135

J&J

($ millions)	2001	2002A	2003A	2004E	2005E	2006E	2007E	2008E
	$956	**$1,191**	**$2,178**	**$2,594**	**$2,882**	**$2,795**	**$2,307**	**$2,054**
Coronary Stents	471	687	1,581	1,959	2,187	2,002	1,439	1,122
Radiation Therapy	8	8	8	5	3	2	1	1
Conventional Angioplasty	310	308	379	386	403	421	430	440
Peripheral Stents	162	182	204	235	264	290	320	356
Carotid Stents	5	6	7	9	25	80	117	135

Medtronic

($ millions)	2001	2002A	2003A	2004E	2005E	2006E	2007E	2008E
	$792	**$611**	**$597**	**$606**	**$638**	**$713**	**$874**	**$1,157**
Coronary Stents	580	394	360	317	312	343	485	735
Conventional Angioplasty	185	182	174	225	262	279	265	251
Peripheral Stents	16	19	20	22	25	26	29	30
Carotid Stents	0	0	0	2	6	25	40	55
Embolic Protection	12	17	43	40	28	32	45	70
Vascular Closure	0	0	0	0	$6	$8	$10	$15

Guidant

($ millions)	2001	2002A	2003A	2004E	2005E	2006E	2007E	2008E
	$1,266	**$1,363**	**$1,288**	**$1,020**	**$872**	**$1,132**	**$2,237**	**$2,419**
Coronary Stents	819	874	783	440	222	455	1,540	1,702
Radiation Therapy	5	43	0	0	0	0	0	0
Conventional Angioplasty	387	371	409	432	439	424	412	398
Peripheral Stents	39	53	65	82	95	107	119	134
Carotid Stents	5	8	11	38	80	106	134	154
Atherectomy	11	14	20	29	36	40	32	31

Abbott

($ millions)	2001	2002A	2003A	2004E	2005E	2006E	2007E	2008E
	$115	**$110**	**$110**	**$142**	**$185**	**$272**	**$403**	**$525**
Coronary Stents	25	15	8	29	55	100	200	300
Carotid Stents	0	0	2	5	10	40	60	70
Vascular Closure	90	95	100	108	120	132	143	155

St. Jude

($ millions)	2001	2002A	2003A	2004E	2005E	2006E	2007E	2008E
	$95	**$153**	**$218**	**$288**	**$322**	**$359**	**$395**	**$434**
Vascular Closure	95	153	218	288	322	359	395	434

Source: Morgan Stanley Research

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Morgan Stanley

Exhibit 2

Coronary Stent Estimated U.S. Sales, 2000-2008E

	2000	2001	2002	2003A	2004A	2005E	2006E	2007E	2008E
No. of PTCA Procedures (000)	770	810	850	920	970	1020	1070	1124	1180
% change	6%	5%	5%	8%	5%	5%	5%	5%	5%
% of PTCA Procedures Using Stents	81%	85%	88%	90%	90%	90%	90%	90%	90%
Number of Stent Procedures (000)	624	690	751	828	873	922	966	1016	1066
% change	15%	11%	9%	10%	5%	6%	5%	5%	5%
% of Stent Procedures Using Bare Metal Stents	**100%**	**100%**	**100%**	**67%**	**21%**	**11%**	**5%**	**4%**	**3%**
% of Stent Procedures Using Drug-Eluting Stents	**0%**	**0%**	**0%**	**33%**	**79%**	**90%**	**95%**	**96%**	**97%**
US Bare Metal Stent Market									
Number of Bare Metal Stent Procedures (000)	624	690	751	557	181	97	52	42	34
Stents Per Procedure	1.8	1.7	1.7	1.7	1.7	1.6	1.6	1.6	1.6
Price Per Bare Metal Stent	$1,350	$1,202	$1,121	$900	$950	$600	$600	$550	$530
Total Revenues Per Procedure	$2,381	$2,073	$1,861	$1,486	$1,658	$930	$960	$869	$869
Total US Bare Metal Stent Market *($ millions)*	$1,485	$1,431	$1,397	$828	$300	$90	$50	$36	$30
Stocking *($ millions)*	($59)	$21	($5)	$0	$1	$0	$0	$0	$0
Total US Bare Metal Stent Sales *($ millions)*	**$1,426**	**$1,452**	**$1,392**	**$828**	**$301**	**$90**	**$50**	**$36**	**$30**
% Change	1%	2%	-4%	-41%	-64%	-70%	-44%	-28%	-18%
US Drug-Eluting Stent Market									
Number of Drug-Eluting Stent Procedures (000)	0	0	0	271	692	825	914	974	1032
Stents Per Procedure				1.5	1.6	1.6	1.6	1.6	1.6
Price Per Drug-Eluting Stent				$2,800	$2,525	$2,475	$2,300	$2,225	$2,200
Total Revenues Per Procedure				$4,060	$4,012	$3,977	$3,770	$3,614	$3,479
Total US Drug-Eluting Stent Market ($ millions)				$1,100	$2,778	$3,282	$3,446	$3,520	$3,592
Stocking *($ millions)*				$0	$11	$0	$0	$0	$0
Total US Drug-Eluting Stent Sales ($ millions)				**$1,100**	**$2,789**	**$3,282**	**$3,446**	**$3,520**	**$3,592**
% Change					154%	18%	5%	2%	2%
Total US Stent Market									
Total Number of Stent Procedures (000)	624	690	751	828	873	922	966	1016	1066
Stents Per Procedure	1.8	1.7	1.7	1.6	1.6	1.6	1.6	1.6	1.6
Average Price Per Stent	$1,350	$1,202	$1,121	$1,521	$2,199	$2,278	$2,208	$2,156	$2,147
Total Revenues Per Procedure	$2,381	$2,073	$1,861	$5,546	$5,670	$4,907	$4,730	$4,483	$4,349
Total US Stent Market *($ millions)*	**$1,485**	**$1,431**	**$1,397**	**$1,927**	**$3,077**	**$3,372**	**$3,496**	**$3,557**	**$3,621**
Stocking *($ millions)*	($59)	$21	($5)	$0	$12	$0	$0	$0	$0
Total US Stent Sales *($ millions)*	**$1,426**	**$1,452**	**$1,392**	**$1,927**	**$3,089**	**$3,372**	**$3,496**	**$3,557**	**$3,621**
% Change	1%	2%	-4%	39%	60%	9%	4%	2%	2%
Total US Stent Sales By Competitor	**$1,426**	**$1,452**	**$1,392**	**$1,928**	**$3,090**	**$3,372**	**$3,496**	**$3,556**	**$3,622**
Bare Metal	**$1,426**	**$1,452**	**$1,392**	**$828**	**$301**	**$90**	**$50**	**$36**	**$30**
Boston Scientific	$248	$182	$180	$213	$62	$18	$5	$5	$5
Guidant[1]	$594	$585	$576	$402	$162	$45	$15	$10	$10
Johnson & Johnson	$148	$309	$387	$75	$18	$15	$10	$10	$5
Medtronic	$418	$356	$197	$118	$59	$12	$20	$11	$10
Other	$18	$20	$52	$20	$0	$0	$0	$0	$0
Drug-Eluting				**$1,100**	**$2,789**	**$3,282**	**$3,446**	**$3,520**	**$3,592**
Boston Scientific				$0	$1,570	$2,080	$2,125	$1,265	$1,170
Guidant[1]				$0	$0	$0	$0	$1,000	$1,137
Johnson & Johnson				$1,100	$1,219	$1,202	$1,321	$944	$757
Medtronic				$0	$0	$0	$0	$190	$330
Other				$0	$0	$0	$0	$121	$198
US Stent Market Shares									
Bare Metal	100%	100%	100%	100%	100%	100%	100%	100%	100%
Boston Scientific	17%	13%	13%	26%	21%	20%	10%	14%	17%
Guidant	42%	40%	41%	49%	54%	50%	30%	28%	33%
Johnson & Johnson	10%	21%	28%	9%	6%	17%	20%	28%	17%
Medtronic	29%	25%	14%	14%	20%	13%	40%	31%	33%
Other	1%	1%	4%	2%	0%	0%	0%	0%	0%
Drug-Eluting				100%	100%	100%	100%	100%	100%
Boston Scientific				0%	56%	63%	62%	36%	33%
Guidant				0%	0%	0%	0%	28%	32%
Johnson & Johnson				100%	44%	37%	38%	27%	21%
Medtronic				0%	0%	0%	0%	5%	9%
Other				0%	0%	0%	0%	3%	6%

E = Morgan Stanley Research Estimate

[1] *Guidant's revenues in this model reflect end-user sales only. This excludes component sales to JNJ, which the company includes in its reported coronary stent revenues in the US.*

Source: Morgan Stanley Research

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Exhibit 3

Coronary Stent Estimated International Sales, 2000-2008E

	2000	2001	2002	2003A	2004A	2005E	2006E	2007E	2008E
No. of PTCA Procedures (000)	702	804	951	1063	1151	1241	1339	1445	1432
% change	11%	15%	18%	12%	8%	8%	8%	8%	-1%
% of PTCA Procedures Using Stents	68%	72%	74%	74%	78%	80%	80%	81%	82%
Number of Stent Procedures (000)	480	576	708	788	892	989	1072	1168	1179
% change	19%	20%	23%	11%	13%	11%	8%	9%	1%
% of Stent Procedures Using Bare Metal Stents	**100%**	**100%**	**95%**	**72%**	**47%**	**31%**	**21%**	**16%**	**13%**
% of Stent Procedures Using Drug-Eluting Stents	**0%**	**0%**	**5%**	**28%**	**53%**	**69%**	**79%**	**84%**	**87%**
OUS Bare Metal Stent Market									
Number of Bare Metal Stent Procedures (000)	480	576	672	567	423	308	227	188	155
Stents Per Procedure	1.3	1.3	1.3	1.4	1.6	1.6	1.6	1.6	1.6
Price Per Bare Metal Stent	$1,335	$1,147	$1,047	$1,179	$1,167	$1,014	$853	$834	$832
Total Revenues Per Procedure	$1,698	$1,439	$1,334	$1,684	$1,890	$1,608	$1,402	$1,367	$1,369
Total OUS Bare Metal Stent Market *($ millions)*	$815	$838	$907	$948	$802	$498	$319	$257	$213
Stocking *($ millions)*	$0	($4)	$1	$0	$7	$0	$0	$0	$0
Total OUS Bare Metal Stent Sales *($ millions)*	**$815**	**$834**	**$907**	**$948**	**$809**	**$498**	**$319**	**$257**	**$213**
% Change	12%	2%	9%	4%	-15%	-38%	-36%	-19%	-17%
OUS Drug-Eluting Stent Market									
Number of Drug-Eluting Stent Procedures (000)	0	0	36	222	469	680	845	980	1023
Stents Per Procedure			1.3	1.4	1.5	1.5	1.5	1.5	1.5
Price Per Drug-Eluting Stent			$1,650	$1,645	$1,744	$1,741	$1,527	$1,401	$1,302
Total Revenues Per Procedure			$2,063	$2,229	$2,673	$2,633	$2,312	$2,089	$1,967
Total OUS Drug-Eluting Stent Market ($ millions)			$74	$494	$1,245	$1,759	$1,918	$2,034	$1,982
Stocking *($ millions)*			$0	$0	$6	$0	$0	$0	$0
Total OUS Drug-Eluting Stent Sales ($ millions)			**$74**	**$494**	**$1,251**	**$1,759**	**$1,918**	**$2,034**	**$1,982**
% Change				565%	153%	41%	9%	6%	-3%
Total OUS Stent Market									
Total Number of Stent Procedures (000)	480	576	708	788	892	989	1072	1168	1179
Stents Per Procedure	1.3	1.3	1.3	1.4	1.6	1.5	1.5	1.5	1.5
Average Price Per Stent	$1,335	$1,147	$1,078	$1,310	$1,470	$1,514	$1,384	$1,310	$1,240
Total Revenues Per Procedure	$1,698	$1,439	$1,372	$1,844	$2,314	$2,325	$2,133	$1,984	$1,895
Total OUS Stent Market *($ millions)*	$815	$838	$981	$1,442	$2,047	$2,256	$2,236	$2,291	$2,195
Stocking *($ millions)*	$0	($4)	$1	$0	$13	$0	$0	$0	$0
Total OUS Stent Sales *($ millions)*	**$815**	**$834**	**$982**	**$1,442**	**$2,060**	**$2,256**	**$2,236**	**$2,291**	**$2,195**
% Change	12%	2%	18%	47%	43%	10%	-1%	2%	-4%
Total OUS Stent Sales By Competitor	**$815**	**$834**	**$981**	**$1,442**	**$2,060**	**$2,256**	**$2,236**	**$2,291**	**$2,195**
Bare Metal	**$815**	**$834**	**$907**	**$948**	**$808**	**$498**	**$319**	**$257**	**$213**
Boston Scientific	$181	$162	$138	$115	$146	$82	$44	$37	$30
Guidant	$227	$234	$298	$381	$278	$177	$110	$80	$55
Johnson & Johnson	$112	$162	$230	$130	$78	$50	$25	$20	$15
Medtronic	$220	$224	$197	$242	$276	$159	$121	$95	$83
Other	$75	$52	$43	$80	$30	$30	$19	$25	$30
Drug-Eluting			**$74**	**$494**	**$1,252**	**$1,758**	**$1,917**	**$2,034**	**$1,982**
Boston Scientific			$0	$199	$573	$595	$509	$635	$516
Guidant			$0	$0	$0	$0	$330	$450	$500
Johnson & Johnson			$70	$276	$644	$920	$646	$465	$345
Medtronic			$0	$0	$0	$150	$229	$229	$367
Other			$4	$19	$35	$93	$203	$255	$254
OUS Stent Market Shares									
Bare Metal	100%	100%	100%	100%	100%	100%	100%	100%	100%
Boston Scientific	22%	19%	15%	12%	18%	16%	14%	14%	14%
Guidant	28%	28%	33%	40%	34%	36%	34%	31%	26%
Johnson & Johnson	14%	19%	25%	14%	10%	10%	8%	8%	7%
Medtronic	27%	27%	22%	26%	34%	32%	38%	37%	39%
Other	9%	6%	5%	8%	4%	6%	6%	10%	14%
Drug-Eluting			100%	100%	100%	100%	100%	100%	100%
Boston Scientific			0%	40%	46%	34%	27%	31%	26%
Guidant			0%	0%	0%	0%	17%	22%	25%
Johnson & Johnson			95%	56%	51%	52%	34%	23%	17%
Medtronic			0%	0%	0%	9%	12%	11%	19%
Other			5%	4%	3%	5%	11%	13%	13%

E = Morgan Stanley Research Estimate
Source: Morgan Stanley Research

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Exhibit 4

Coronary Stent Estimated Worldwide Sales, 2000-2008E

	2000	2001	2002A	2003A	2004A	2005E	2006E	2007E	2008E
No. of Stent Procedures (000)	1103	1266	1459	1616	1765	1911	2038	2184	2245
% change	17%	15%	15%	11%	9%	8%	7%	7%	3%
Stents per Procedure	1.5	1.5	1.5	1.5	1.6	1.6	1.6	1.6	1.6
Price Per Stent	$1,345	$1,185	$1,108	$1,391	$1,817	$1,880	$1,772	$1,711	$1,666
% change	-6%	-12%	-7%	26%	31%	3%	-6%	-3%	-3%
Revenue Per Procedure	$2,084	$1,791	$1,630	$2,085	$2,903	$2,945	$2,812	$2,677	$2,591
% change	-8%	-14%	-9%	28%	39%	1%	-5%	-5%	-3%
Total Worldwide Stent Market *($ millions)*	$2,300	$2,269	$2,378	$3,370	$5,124	$5,629	$5,732	$5,848	$5,816
Stocking *($ millions)*	($59)	$17	($5)	$0	$25	$0	$0	$0	$0
Total Worldwide Stent Sales *($ millions)*	**$2,241**	**$2,286**	**$2,373**	**$3,370**	**$5,149**	**$5,629**	**$5,732**	**$5,848**	**$5,816**
% change	5%	2%	4%	42%	53%	9%	2%	2%	-1%
WW Revenues By Competitor *($ millions)*	**$2,241**	**$2,286**	**$2,372**	**$3,370**	**$5,150**	**$5,628**	**$5,732**	**$5,847**	**$5,817**
Boston Scientific	$429	$344	$318	$527	$2,351	$2,775	$2,683	$1,942	$1,721
Guidant	$821	$819	$874	$783	$440	$222	$455	$1,540	$1,702
Johnson & Johnson	$260	$471	$687	$1,581	$1,959	$2,187	$2,002	$1,439	$1,122
Medtronic	$638	$580	$394	$360	$335	$321	$370	$525	$790
Other	$93	$72	$99	$119	$65	$123	$222	$401	$482
WW Market Shares	100%	100%	100%	100%	100%	100%	100%	100%	100%
Boston Scientific	19%	15%	13%	16%	46%	49%	47%	33%	30%
Guidant	37%	36%	37%	23%	9%	4%	8%	26%	29%
Johnson & Johnson	12%	21%	29%	47%	38%	39%	35%	25%	19%
Medtronic	28%	25%	17%	11%	7%	6%	6%	9%	14%
Other	4%	3%	4%	4%	1%	2%	4%	7%	8%

E = Morgan Stanley Research Estimate

Source: Morgan Stanley Research

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Exhibit 5

PTCA Estimated U.S. Sales, 2001-2008E

United States	2000	2001A	2002A	2003A	2004E	2005E	2006E	2007E
No. of PTCA Procedures (000)	770	810	850	920	970	1,020	1,070	1,124
% Change	6%	5%	5%	8%	5%	5%	5%	5%
Total Accessory Revenue *($ millions)*	$285	$292	$289	$304	$320	$337	$337	$348
Total Revenue Per Procedure	$810	$820	$790	$820	$820	$820	$790	$760
% Change	-6%	1%	-4%	4%	0%	0%	-4%	-4%
Total U.S. PTCA & Acc. Sales *($ millions)*	**$627**	**$666**	**$671**	**$753**	**$794**	**$832**	**$847**	**$858**
% Change	1%	6%	1%	12%	5%	5%	2%	1%
US Revenues By Competitor *($ millions)*	**$627**	**$666**	**$671**	**$753**	**$794**	**$832**	**$848**	**$858**
Boston Scientific	$246	$283	$301	$372	$407	$433	$455	$478
Guidant	$188	$199	$190	$202	$206	$206	$197	$188
Johnson & Johnson	$103	$105	$103	$106	$98	$98	$98	$98
Medtronic	$69	$64	$62	$61	$71	$82	$86	$81
Other	$21	$15	$15	$12	$12	$12	$12	$12
US Market Shares								
Boston Scientific	39%	43%	45%	49%	51%	52%	54%	56%
Guidant	30%	30%	28%	27%	26%	25%	23%	22%
Johnson & Johnson	16%	16%	15%	14%	12%	12%	12%	11%
Medtronic	11%	10%	9%	8%	9%	10%	10%	9%
Other	3%	2%	2%	2%	2%	1%	1%	1%
Total	100%	100%	100%	100%	100%	100%	100%	100%

Source: Morgan Stanley Research

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Exhibit 6

PTCA Estimated International Sales, 2001-2008E

($ Millions)

International	2000	2001A	2002A	2003A	2004E	2005E	2006E	2007E	2008E
European PTCA Procedures (000)	376	434	521	583	636	687	742	801	865
% change	9%	16%	20%	12%	9%	8%	8%	8%	8%
Japanese PTCA Procedures (000)	132	142	150	158	164	172	181	190	199
% change	9%	8%	6%	5%	4%	5%	5%	5%	5%
Rest of World PTCA Procedures (000)	195	230	281	321	352	383	417	455	496
% change	17%	18%	22%	15%	10%	9%	9%	9%	9%
Total Int'l PTCA Procedures (000)	703	806	951	1062	1151	1241	1339	1445	1560
% change	11%	15%	18%	12%	8%	8%	8%	8%	8%
Revenue per Procedure	$1,275	$1,215	$1,094	$1,077	$1,066	$1,042	$992	$924	$862
% change	-4%	-5%	-10%	-2%	-1%	-2%	-5%	-7%	-7%
Total Int'l PTCA Sales *($ millions)*	**$896**	**$979**	**$1,040**	**$1,144**	**$1,228**	**$1,293**	**$1,329**	**$1,336**	**$1,345**
% change	7%	9%	6%	10%	7%	5%	3%	1%	1%
	571	664	801	905	988	1069	1159	1256	1361
OUS Revenues By Competitor *($ millions)*	**$896**	**$979**	**$1,039**	**$1,144**	**$1,228**	**$1,293**	**$1,329**	**$1,336**	**$1,345**
Boston Scientific	$303	$310	$308	$320	$345	$359	$371	$382	$395
Guidant	$172	$188	$181	$207	$226	$233	$227	$224	$218
Johnson & Johnson	$202	$205	$205	$273	$288	$305	$323	$332	$342
Medtronic	$104	$121	$120	$113	$154	$180	$193	$183	$174
Other	$115	$155	$225	$230	$215	$215	$215	$215	$215
OUS Market Shares	100%	100%	100%	100%	100%	100%	100%	100%	100%
Boston Scientific	34%	32%	30%	28%	28%	28%	28%	29%	29%
Guidant	19%	19%	17%	18%	18%	18%	17%	17%	16%
Johnson & Johnson	23%	21%	20%	24%	23%	24%	24%	25%	25%
Medtronic	12%	12%	12%	10%	13%	14%	15%	14%	13%
Other	13%	16%	22%	20%	18%	17%	16%	16%	16%

E = Morgan Stanley Research Estimate
Source: Morgan Stanley Research

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Exhibit 7

PTCA Estimated Worldwide Sales, 2001-2008E

Worldwide	2001A	2002A	2003A	2004E	2005E	2006E	2007E	2008E
No. of PTCA Procedures (000)	1616	1801	1982	2121	2261	2409	2569	2740
% change	10%	11%	10%	7%	7%	7%	7%	7%
Revenue per Procedure	$1,018	$950	$957	$953	$940	$903	$854	$807
% change	-2%	-7%	1%	0%	-1%	-4%	-5%	-5%
Total Worldwide PTCA Sales *($ millions)*	**$1,645**	**$1,712**	**$1,896**	**$2,022**	**$2,125**	**$2,176**	**$2,195**	**$2,212**
% change	8%	4%	11%	7%	5%	2%	1%	1%
WW Revenues By Competitor *($ millions)*	**$1,645**	**$1,710**	**$1,897**	**$2,022**	**$2,124**	**$2,177**	**$2,194**	**$2,211**
Boston Scientific	$593	$609	$692	$752	$793	$826	$860	$895
Guidant	$387	$371	$409	$432	$439	$424	$412	$398
Johnson & Johnson	$310	$308	$379	$386	$403	$421	$430	$440
Medtronic	$185	$182	$174	$225	$262	$279	$265	$251
Other	$170	$240	$242	$227	$227	$227	$227	$227
WW Market Shares	100%	100%	100%	100%	100%	100%	100%	100%
Boston Scientific	36%	36%	37%	37%	37%	38%	39%	40%
Guidant	24%	22%	22%	21%	21%	19%	19%	18%
Johnson & Johnson	19%	18%	20%	19%	19%	19%	20%	20%
Medtronic	11%	11%	9%	11%	12%	13%	12%	11%
Other	10%	14%	13%	11%	11%	10%	10%	10%

E = Morgan Stanley Research Estimate

Source: Morgan Stanley Research

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Exhibit 8

In-Stent Restenosis (Brachytherapy) Estimated Worldwide Sales, 2001-2008E

In-Stent Restenosis
Estimated Worldwide Market, 2001-2008E

($ millions)	2001	2002	2003	2004E	2005E	2006E	2007E	2008E
Total Worldwide Market	**$83**	**$120**	**$71**	**$29**	**$17**	**$12**	**$9**	**$7**
Guidant	$5	$43	$0	$0	$0	$0	$0	$0
Johnson & Johnson	$8	$8	$8	$5	$3	$2	$1	$1
Novoste	$70	$69	$63	$24	$14	$10	$8	$6
	01/00	02/01	03/02	04/03	05/04	06/05	07/06	07/08
Worldwide Market Growth	nm	**44%**	**-41%**	**-59%**	**-40%**	**-31%**	**-25%**	**-18%**
Guidant	nm	nm	nm	nm	nm	nm	nm	nm
Johnson & Johnson	nm	0%	-3%	-36%	-40%	-33%	-50%	0%
Novoste	nm	-1%	-9%	-62%	-40%	-30%	-20%	-20%
($ millions)	2001	2002	2003A	2004E	2005E	2006E	2007E	2008E
Total US Market Shares	100%	100%	100%	100%	100%	100%	100%	100%
Guidant	6%	36%	0%	0%	0%	0%	0%	0%
Johnson & Johnson	10%	7%	11%	17%	17%	17%	11%	13%
Novoste	84%	58%	89%	83%	83%	83%	89%	87%

Source: Morgan Stanley Research

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Exhibit 9

Embolic Protection Worldwide Estimated Sales, 2001-2008E

Distal Protection

Estimated Worldwide Market, 2001-2008E

($ millions)	2001	2002	2003A	2004E	2005E	2006E	2007E	2008E
Total Worldwide Market	**$18**	**$35**	**$80**	**$97**	**$106**	**$152**	**$215**	**$280**
Boston Scientific	$2	$13	$32	$51	$65	$95	$125	$155
Medtronic	$12	$17	$43	$40	$28	$32	$45	$70
EV3	$0	$1	$2	$4	$8	$22	$41	$53
Other	$4	$4	$3	$3	$5	$3	$4	$2
	01/00	02/01	03/02	04/03	05/04	06/05	07/06	07/08
Worldwide Market Growth	**NM**	**NM**	**NM**	**22%**	**9%**	**43%**	**41%**	**30%**
Boston Scientific	NM	NM	NM	59%	27%	46%	32%	24%
Medtronic	NM	42%	153%	-8%	-29%	14%	41%	56%
EV3	NM	NM	80%	106%	111%	179%	86%	30%
Other	NM	-12%	-26%	16%	67%	-46%	34%	-46%
	2001	2002	2003A	2004E	2005E	2006E	2007E	2008E
Worldwide Market Share	100%	100%	100%	100%	100%	100%	100%	100%
Boston Scientific	11%	37%	40%	52%	61%	63%	58%	55%
Medtronic	65%	49%	54%	41%	26%	21%	21%	25%
EV3	0%	3%	2%	4%	7%	14%	19%	19%
Other	24%	11%	4%	3%	5%	2%	2%	1%

Source: Morgan Stanley Research

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Exhibit 10

Carotid Stent Estimated U.S. Sales, 2001-2008E

Year	2001	2002	2003A	2004E	2005E	2006E	2007E	2008E
Total US Carotid Interventions (000)	160	162	170	180	198	218	250	275
% growth	*1%*	*1%*	*5%*	*6%*	*10%*	*10%*	*15%*	*10%*
% Carotid Endorectomy	99%	99%	99%	96%	86%	71%	60%	53%
% Stent	1%	1%	1%	4%	15%	29%	40%	47%
# of Carotid Stent Procedures (000)	2	2	2	8	29	64	100	130
% growth		*-6%*	*5%*	*242%*	*280%*	*122%*	*57%*	*30%*
Revenue per Procedure	$ 2,000	$ 2,500	$ 3,000	$ 3,500	$ 3,500	$ 3,450	$ 3,375	$ 3,300
% growth		*25%*	*20%*	*17%*	*0%*	*-1%*	*-2%*	*-2%*
Revenues ($ millions)	**$ 4**	**$ 5**	**$ 7**	**$ 26**	**$ 100**	**$ 220**	**$ 338**	**$ 430**
% growth		*17%*	*26%*	*300%*	*280%*	*119%*	*54%*	*27%*
US Revenues By Competitor ($ millions)	**$ 4**	**$ 5**	**$ 7**	**$ 26**	**$ 100**	**$ 220**	**$ 338**	**$ 430**
Boston Scientific	$ -	$ -	$ -	$ -	$ 7	$ 25	$ 55	$ 100
Guidant	$ 1	$ 2	$ 3	$ 22	$ 60	$ 80	$ 100	$ 110
Johnson & Johnson	$ 3	$ 3	$ 4	$ 4	$ 15	$ 65	$ 100	$ 110
Medtronic	$ -	$ -	$ -	$ -	$ 3	$ 20	$ 30	$ 40
Other	$ -	$ -	$ -	$ -	$ 15	$ 30	$ 53	$ 70
US Market Shares	100%	100%	100%	100%	100%	100%	100%	100%
Boston Scientific	0%	0%	0%	0%	7%	11%	16%	23%
Guidant	25%	40%	43%	85%	60%	36%	30%	26%
Johnson & Johnson	75%	60%	57%	15%	15%	30%	30%	26%
Medtronic	0%	0%	0%	0%	3%	9%	9%	9%
Other	0%	0%	0%	0%	15%	14%	16%	16%

E = Morgan Stanley Research Estimate

Source: Morgan Stanley Research

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Exhibit 11

Carotid Stent Estimated International Sales, 2001-2008E

Year	2001	2002	2003A	2004E	2005E	2006E	2007E	2008E
Total OUS Carotid Interventions (000)	80	82	86	94	107	120	136	150
% growth	*1%*	*2%*	*5%*	*10%*	*13%*	*13%*	*13%*	*10%*
% Carotid Endorectomy	95%	93%	93%	87%	82%	75%	68%	60%
% Stent	5%	7%	8%	13%	18%	25%	32%	40%
# of Carotid Stent Procedures (000)	4	6	6	12	19	30	44	60
% growth		*20%*	*13%*	*91%*	*56%*	*57%*	*45%*	*38%*
Revenue per Procedure	$ 1,500	$ 2,000	$ 2,500	$ 2,800	$ 2,800	$ 2,750	$ 2,700	$ 2,650
% growth		*33%*	*25%*	*12%*	*0%*	*-2%*	*-2%*	*-2%*
Revenues ($ millions)	**$ 6**	**$ 11**	**$ 16**	**$ 34**	**$ 54**	**$ 83**	**$ 117**	**$ 159**
% growth		*90%*	*41%*	*114%*	*56%*	*54%*	*42%*	*35%*
OUS Revenues By Competitor ($ millions)	**$ 6**	**$ 11**	**$ 16**	**$ 34**	**$ 54**	**$ 83**	**$ 117**	**$ 159**
Boston Scientific	$ -	$ 2	$ 5	$ 5	$ 10	$ 20	$ 25	$ 30
Guidant	$ 4	$ 6	$ 8	$ 16	$ 20	$ 26	$ 34	$ 44
Johnson & Johnson	$ 2	$ 3	$ 3	$ 5	$ 10	$ 15	$ 17	$ 25
Medtronic	$ -	$ -	$ -	$ 2	$ 3	$ 5	$ 10	$ 15
Other	$ -	$ -	$ -	$ 6	$ 11	$ 17	$ 31	$ 45
OUS Market Shares	100%	100%	100%	100%	100%	100%	100%	100%
Boston Scientific	0%	18%	31%	15%	19%	24%	21%	19%
Guidant	67%	55%	50%	47%	37%	31%	29%	28%
Johnson & Johnson	33%	27%	19%	15%	19%	18%	15%	16%
Medtronic	0%	0%	0%	6%	6%	6%	9%	9%
Other	0%	0%	0%	18%	20%	20%	26%	28%

E = Morgan Stanley Research Estimate

Source: Morgan Stanley Research

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Exhibit 12

Carotid Stent Estimated Worldwide Sales, 2001-2008E

Year	2001	2002	2003A	2004E	2005E	2006E	2007E	2008E
Total Carotid Interventions (000)	240	243	255	274	304	338	386	425
% growth	*1%*	*1%*	*5%*	*7%*	*11%*	*11%*	*14%*	*10%*
% Carotid Endarectomy	97%	97%	97%	93%	84%	72%	63%	55%
% Stent	3%	3%	3%	7%	16%	28%	37%	45%
# of Carotid Stent Procedures (000)	6	8	9	20	48	94	144	190
% growth		*25%*	*10%*	*129%*	*142%*	*96%*	*53%*	*32%*
Revenue per Procedure	$ 1,679	$ 2,134	$ 2,628	$ 3,067	$ 3,220	$ 3,226	$ 3,170	$ 3,095
% growth		*27%*	*23%*	*17%*	*5%*	*0%*	*-2%*	*-2%*
Revenues ($ millions)	$ 10	$ 17	$ 23	$ 61	$ 154	$ 303	$ 455	$ 588
% growth		*59%*	*36%*	*168%*	*154%*	*96%*	*50%*	*29%*
Revenues By Competitor ($ millions)								
Boston Scientific	$ -	$ 2	$ 5	$ 5	$ 17	$ 45	$ 80	$ 130
Guidant	$ 5	$ 8	$ 11	$ 38	$ 80	$ 106	$ 134	$ 154
Johnson & Johnson	$ 5	$ 6	$ 7	$ 9	$ 25	$ 80	$ 117	$ 135
Medtronic	$ -	$ -	$ -	$ 2	$ 6	$ 25	$ 40	$ 55
Other	$ -	$ -	$ -	$ 6	$ 26	$ 47	$ 84	$ 115
Market Shares								
Boston Scientific	0%	13%	22%	8%	11%	15%	18%	22%
Guidant	50%	50%	48%	63%	52%	35%	29%	26%
Johnson & Johnson	50%	38%	30%	15%	16%	26%	26%	23%
Medtronic	0%	0%	0%	3%	4%	8%	9%	9%
Other	0%	0%	0%	10%	17%	16%	18%	20%

E = Morgan Stanley Research Estimate

Source: Morgan Stanley Research

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Exhibit 13

Peripheral Stents Estimated U.S. Sales, 2001-2008E

($ millions)	2001	2002	2003	2004E	2005E	2006E	2007E	2008E	02/01	03/02	04/03	05/04	06/05	07/06	08/07
Lower Body															
Iliac	$170	$197	$217	$239	$257	$273	$290	$306	16%	10%	10%	8%	6%	6%	5%
Femoral/Popliteal	$25	$27	$31	$37	$47	$61	$79	$99	10%	15%	20%	25%	30%	30%	25%
Upper Body															
Renal/Subclavian	$70	$81	$93	$113	$141	$162	$187	$205	15%	15%	22%	25%	15%	15%	10%
Total US Market	**$264**	**$305**	**$341**	**$390**	**$445**	**$496**	**$556**	**$610**	**15%**	**12%**	**14%**	**14%**	**11%**	**12%**	**10%**
Total US Market	**$264**	**$305**	**$341**	**$390**	**$445**	**$496**	**$556**	**$610**							
Johnson & Johnson	$113	$131	$149	$170	$191	$210	$232	$259	16%	13%	14%	12%	10%	10%	12%
Boston Scientific	$94	$99	$100	$102	$107	$112	$118	$124	6%	1%	2%	5%	5%	5%	5%
Guidant	$31	$42	$48	$59	$68	$75	$81	$87	33%	15%	23%	15%	11%	7%	8%
Medtronic	$8	$11	$14	$15	$17	$18	$20	$20	36%	33%	10%	10%	6%	11%	0%
CR Bard	$13	$15	$20	$31	$37	$41	$45	$49	15%	33%	55%	20%	10%	10%	10%
EV3	$6	$6	$8	$10	$12	$20	$30	$40	0%	33%	25%	20%	67%	50%	20%
Other	$0	$2	$2	$2	$13	$20	$30	$30	NM	NM	NM	NM	54%	50%	0%
Total US Market Shares	100%	100%	100%	100%	100%	100%	100%	100%							
Johnson & Johnson	43%	43%	44%	44%	43%	42%	42%	42%							
Boston Scientific	35%	32%	29%	26%	24%	23%	21%	20%							
Guidant	12%	14%	14%	15%	15%	15%	15%	14%							
Medtronic	3%	3%	4%	4%	4%	4%	4%	3%							
CR Bard	5%	5%	6%	8%	8%	8%	8%	8%							
EV3 (IntraTherapeutics)	2%	2%	2%	3%	3%	4%	5%	7%							
Other	0%	1%	1%	1%	3%	4%	5%	5%							

Source: Company data, Morgan Stanley Research

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Exhibit 14

Peripheral Stents Estimated International Sales, 2001-2008E

($ millions)	2001	2002	2003	2004E	2005E	2006E	2007E	2008E	02/01	03/02	04/03	05/04	06/05	07/06	08/07
Lower Body															
Iliac	$90	$95	$104	$116	$123	$130	$136	$143	5%	10%	11%	7%	5%	5%	5%
Femoral/Popliteal	$25	$26	$32	$40	$49	$62	$74	$85	5%	20%	25%	25%	25%	20%	15%
Upper Body															
Renal/Subclavian	$30	$33	$40	$50	$59	$71	$82	$94	10%	20%	25%	20%	20%	15%	15%
Total OUS Market	**$145**	**$154**	**$176**	**$205**	**$232**	**$263**	**$292**	**$322**	**6%**	**14%**	**17%**	**13%**	**13%**	**11%**	**10%**
Total OUS Market	**$145**	**$154**	**$176**	**$205**	**$232**	**$263**	**$292**	**$322**	6%	14%	17%	13%	13%	11%	10%
Johnson & Johnson	$49	$51	$55	$65	$73	$80	$88	$97	4%	8%	18%	12%	10%	10%	10%
Boston Scientific	$47	$53	$66	$70	$77	$81	$86	$91	12%	25%	7%	10%	5%	6%	6%
Guidant	$8	$11	$17	$22	$27	$32	$38	$46	40%	53%	31%	21%	18%	20%	21%
Medtronic	$8	$8	$6	$7	$8	$8	$9	$10	0%	-25%	17%	10%	10%	10%	10%
CR Bard	$22	$21	$22	$29	$33	$37	$40	$44	-5%	5%	32%	15%	10%	10%	10%
EV3 (IntraTherapeutics)	$6	$6	$8	$10	$12	$20	$25	$30	0%	33%	25%	20%	67%	25%	20%
Other	$5	$4	$2	$2	$2	$5	$5	$3	NM	NM	NM	0%	NM	NM	NM
Total OUS Market Shares	100%	100%	100%	100%	100%	100%	100%	100%							
Johnson & Johnson	34%	33%	31%	32%	31%	30%	30%	30%							
Boston Scientific	32%	34%	37%	34%	33%	31%	29%	28%							
Guidant	6%	7%	10%	11%	12%	12%	13%	14%							
Medtronic	6%	5%	3%	3%	3%	3%	3%	3%							
CR Bard	15%	14%	13%	14%	14%	14%	14%	14%							
EV3 (IntraTherapeutics)	4%	4%	5%	5%	5%	8%	9%	9%							
Other	2%	1%	1%	1%	0%	1%	1%	0%							

Source: Company data, Morgan Stanley Research

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Exhibit 15

Peripheral Stents Estimated Worldwide Sales, 2001-2008E

($ millions)	2001	2002	2003	2004E	2005E	2006E	2007E	2008E	02/01	03/02	04/03	05/04	06/05	07/06	08/07
Lower Body															
Iliac	$260	$292	$321	$355	$381	$403	$427	$449	12%	10%	11%	7%	6%	6%	5%
Femoral/Popliteal	$50	$53	$63	$77	$96	$122	$153	$183	8%	18%	23%	25%	28%	25%	20%
Upper Body															
Renal/Subclavian	$100	$114	$132	$163	$201	$234	$269	$300	14%	16%	23%	23%	16%	15%	12%
Total Worldwide Market	**$409**	**$459**	**$516**	**$595**	**$677**	**$759**	**$848**	**$932**	**12%**	**13%**	**15%**	**14%**	**12%**	**12%**	**10%**
Total WW Market	**$409**	**$459**	**$516**	**$595**	**$677**	**$759**	**$848**	**$931**							
Johnson & Johnson	$162	$182	$204	$235	$264	$290	$320	$356	13%	12%	15%	12%	10%	10%	11%
Boston Scientific	$141	$152	$166	$172	$184	$193	$204	$215	8%	9%	4%	7%	5%	6%	5%
Guidant	$39	$53	$65	$82	$95	$107	$119	$134	35%	23%	25%	17%	13%	11%	12%
Medtronic	$16	$19	$20	$22	$25	$26	$29	$30	18%	8%	12%	10%	7%	11%	3%
CR Bard	$35	$36	$42	$60	$70	$77	$85	$94	3%	17%	43%	17%	10%	10%	10%
EV3 (IntraTherapeutics)	$12	$12	$16	$20	$24	$40	$55	$70	0%	33%	25%	20%	67%	38%	27%
Other	$5	$6	$4	$4	$15	$25	$35	$33	NM	NM	0%	275%	67%	40%	-6%
Total OUS Market Shares	100%	100%	100%	100%	100%	100%	100%	100%							
Johnson & Johnson	39%	40%	39%	39%	39%	38%	38%	38%							
Boston Scientific	34%	33%	32%	29%	27%	25%	24%	23%							
Guidant	10%	12%	13%	14%	14%	14%	14%	14%							
Medtronic	4%	4%	4%	4%	4%	3%	3%	3%							
CR Bard	9%	8%	8%	10%	10%	10%	10%	10%							
EV3 (IntraTherapeutics)	3%	3%	3%	3%	4%	5%	6%	8%							
Other	1%	1%	1%	1%	2%	3%	4%	4%							

Source: Company data, Morgan Stanley Research

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Exhibit 16

Atherectomy Estimated Worldwide Sales, 2001-2008E

($ millions)		2001	2002	2003A	2004E	2005E	2006E	2007E	2008E	02/01	03/02	04/03	05/04	06/05	07/06	08/07
US																
Boston Scientific	IVT Cutting Balloon	$70	$125	$96	$60	$48	$43	$39	$35	79%	-23%	-38%	-20%	-10%	-9%	-10%
	Rotoblator	$45	$31	$25	$22	$14	$11	$11	$11	-31%	-19%	-12%	-36%	-21%	0%	0%
Guidant	DCA	$4	$3	$2	$1	$1	$1	$1	$1	-20%	-53%	-20%	-10%	-10%	-10%	-10%
	X-Tech Cutting Balloon	$0	$0	$2	$6	$10	$12	$10	$10	NM	NM	NM	67%	20%	-17%	0%
Total US Market		$119	$159	$125	$89	$73	$67	$61	$57	34%	-22%	-28%	-18%	-8%	-9%	-7%
US Share																
Boston Scientific		97%	98%	97%	92%	85%	81%	82%	81%							
Guidant		3%	2%	3%	8%	15%	19%	18%	19%							

Estimated International Market, 2001-2008E

($ millions)		2001	2002	2003A	2004E	2005E	2006E	2007E	2008E	02/01	03/02	04/03	05/04	06/05	06/05	06/05
Boston Scientific	IVT Cutting Balloon	$20	$35	$52	$38	$30	$27	$27	$27	75%	49%	-27%	-21%	-10%	0%	0%
	Rotoblator	$35	$33	$27	$17	$14	$12	$12	$11	-6%	-18%	-37%	-18%	-14%	0%	-8%
Guidant	DCA	$11	$14	$14	$13	$10	$8	$6	$5	28%	-2%	-5%	-24%	-20%	-25%	-17%
	X-Tech Cutting Balloon	$0	$0	$2	$4	$6	$8	$6	$6	NM	NM	100%	50%	33%	-25%	0%
Total		$66	$82	$95	$72	$60	$55	$51	$49	24%	15%	-24%	-17%	-8%	-7%	-4%
International Share																
Boston Scientific		83%	83%	83%	76%	73%	71%	76%	78%							
Guidant		17%	17%	17%	24%	27%	29%	24%	22%							

Estimated Worldwide Market, 2001-2008E

($ millions)		2001	2002	2003A	2004E	2005E	2006E	2007E	2008E	02/01	03/02	04/03	05/04	06/05	06/05	06/05
Boston Scientific	IVT Cutting Balloon	$90	$160	$148	$98	$78	$70	$66	$62	78%	-8%	-34%	-20%	-10%	-6%	-6%
	Rotoblator	$80	$64	$52	$39	$28	$23	$23	$22	-20%	-19%	-25%	-28%	-18%	0%	-4%
Guidant	DCA	$15	$17	$15	$14	$11	$9	$7	$6	15%	-11%	-6%	-23%	-19%	-23%	-16%
	X-Tech Cutting Balloon	$0	$0	$4	$10	$16	$20	$16	$16	NM	NM	150%	60%	25%	-20%	0%
Total		$185	$241	$219	$161	$133	$122	$112	$106	30%	-9%	-26%	-18%	-8%	-8%	-5%

Source: Morgan Stanley Research

Exhibit 17

Intravascular Ultrasound Estimated U.S. Sales, 2001-2008E

($ millions)	2001	2002	2003A	2004E	2005E	2006E	2007E	2008E
US IVUS Procedures (000's)	73	83	91	100	109	119	130	141
% Growth	NM	*14%*	*10%*	*10%*	*9%*	*9%*	*9%*	*9%*
Total US Market	**$48**	**$57**	**$71**	**$78**	**$88**	**$99**	**$108**	**$117**
Catheter Revenues	*$40*	*$46*	*$59*	*$65*	*$71*	*$77*	*$84*	*$92*
Console Revenues	*$8*	*$11*	*$12*	*$13*	*$17*	*$22*	*$24*	*$25*
Company Totals	**$47**	**$57**	**$71**	**$78**	**$88**	**$99**	**$108**	**$117**
Boston Scientific	S27	$34	$46	$46	$50	$54	$58	$62
Volcano	S20	$23	$25	$32	$38	$45	$50	$55
Terumo	$0	$0	$0	$0	$0	$0	$0	$0

	01/00	02/01	03/02	04/03	05/04	06/05	07/06	08/07
US Market Growth	**NM**	**18%**	**26%**	**9%**	**13%**	**13%**	**9%**	**8%**
Boston Scientific	NM	26%	35%	0%	9%	8%	7%	7%
Volcano	NM	15%	9%	26%	20%	18%	11%	10%
Terumo	NM	NM	NM	NM	NM	NM	NM	NM

	2001	2002	2003A	2004E	2005E	2006E	2007E	2008E
US Market Share	100%	100%	100%	100%	100%	100%	100%	100%
Boston Scientific	57%	60%	65%	59%	57%	55%	54%	53%
Volcano	43%	40%	35%	41%	43%	45%	46%	47%
Terumo	0%	0%	0%	0%	0%	0%	0%	0%

Source: Company data, Morgan Stanley Research

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Exhibit 18

Intravascular Ultrasound Estimated International Sales, 2001-2008E

($ millions)	2001	2002	2003A	2004E	2005E	2006E	2007E	2008E
Int'l IVUS Procedures (000's)	66	80	101	120	138	158	178	199
% Growth	nm	*21%*	*26%*	*19%*	*15%*	*15%*	*12%*	*12%*
Total International Market	**$64**	**$76**	**$116**	**$146**	**$172**	**$185**	**$198**	**$212**
Catheter Revenues	*$49*	*$63*	*$88*	*$114*	*$147*	*$170*	*$188*	*$207*
Console Revenues	*$15*	*$13*	*$28*	*$32*	*$25*	*$15*	*$10*	*$5*
Company Totals	**$67**	**$78**	**$116**	**$146**	**$172**	**$185**	**$198**	**$212**
Boston Scientific	S42	$50	$88	$111	$122	$128	$134	$141
Volcano	S12	$13	$13	$18	$30	$35	$40	$45
Terumo	S13	$15	$15	$18	$20	$22	$24	$26

	01/00	02/01	03/02	04/03	05/04	06/05	07/06	08/07
International Market Growth	**NM**	**19%**	**53%**	**25%**	**18%**	**7%**	**7%**	**7%**
Boston Scientific	NM	19%	76%	26%	10%	5%	5%	5%
Volcano	NM	8%	-4%	40%	73%	16%	14%	13%
Terumo	NM	14%	2%	16%	14%	10%	9%	8%

	2001	2002	2003A	2004E	2005E	2006E	2007E	2008E
International Market Share	100%	100%	100%	100%	100%	100%	100%	100%
Boston Scientific	37%	37%	47%	50%	47%	45%	44%	43%
Volcano	11%	10%	7%	8%	12%	12%	13%	14%
Terumo	11%	11%	8%	8%	8%	8%	8%	8%

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Exhibit 19

Intravascular Ultrasound Estimated Worldwide Sales, 2001-2008E

($ millions)	2001	2002	2003A	2004E	2005E	2006E	2007E	2008E
WW IVUS Procedures (000's)	139	162	192	220	247	277	308	340
% Growth	NM	*17%*	*18%*	*15%*	*12%*	*12%*	*11%*	*11%*
Total Worldwide Market	**$112**	**$133**	**$187**	**$223**	**$260**	**$284**	**$306**	**$329**
Catheter Revenues	*$89*	*$109*	*$147*	*$179*	*$218*	*$247*	*$272*	*$299*
Console Revenues	*$23*	*$24*	*$40*	*$45*	*$42*	*$37*	*$34*	*$30*
Company Totals	**$114**	**$135**	**$187**	**$224**	**$260**	**$284**	**$306**	**$329**
Boston Scientific	S69	$84	$134	$157	$172	$182	$192	$203
Volcano	S32	$36	$38	$49	$68	$80	$90	$100
Terumo	S13	$15	$15	$18	$20	$22	$24	$26

	01/00	02/01	03/02	04/03	05/04	06/05	07/06	08/07
Worldwide Market Growth	**NM**	**18%**	**41%**	**19%**	**17%**	**9%**	**8%**	**7%**
Boston Scientific	NM	22%	60%	17%	10%	6%	5%	6%
Volcano	NM	13%	4%	31%	39%	17%	13%	11%
Terumo	NM	14%	2%	16%	14%	10%	9%	8%

	2001	2002	2003A	2004E	2005E	2006E	2007E	2008E
Worldwide Market Share	100%	100%	100%	100%	100%	100%	100%	100%
Boston Scientific	61%	62%	72%	70%	66%	64%	63%	62%
Volcano	28%	27%	20%	22%	26%	28%	29%	30%
Terumo	11%	11%	8%	8%	8%	8%	8%	8%

Source: Morgan Stanley Research

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Exhibit 20

Interventional Pharmaceuticals Estimated Worldwide Sales, 2003-2008E

($ millions)	2003	2004E	2005E	2006E	2007E	2008E
Total WW Market	**$5,357**	**$6,844**	**$7,818**	**$8,759**	**$9,511**	**$10,201**
GP IIb/IIIa Inhibitors	*$766*	*$772*	*$781*	*$804*	*$812*	*$819*
Aggrastat	96	84	91	96	102	108
Integrilin	306	325	346	381	399	415
ReoPro	364	363	345	327	311	296
Anti-Thrombins	*$2,124*	*$2,745*	*$2,998*	*$3,419*	*$3,787*	*$4,196*
Angiomax	86	147	212	299	355	420
Lovenox	2,038	2,598	2,786	3,120	3,432	3,776
Oral Platelet Inhibitors	*$2,467*	*$3,327*	*$4,039*	*$4,536*	*$4,912*	*$5,186*
Plavix	2,467	3,327	4,039	4,536	4,912	5,186

	2003	2004E	2005E	2006E	2007E	2008E
WW Market Growth	**23%**	**28%**	**14%**	**12%**	**9%**	**7%**
GP IIb/IIIa Inhibitors	*-5%*	*1%*	*1%*	*3%*	*1%*	*1%*
Aggrastat	-17%	-13%	8%	6%	6%	6%
Integrilin	1%	6%	6%	10%	5%	4%
ReoPro	-5%	0%	-5%	-5%	-5%	-5%
Anti-Thrombins	*27%*	*29%*	*9%*	*14%*	*11%*	*11%*
Angiomax	*123%*	*72%*	44%	41%	19%	18%
Lovenox	24%	27%	7%	12%	10%	10%
Oral Platelet Inhibitors	*31%*	*35%*	*21%*	*12%*	*8%*	*6%*
Plavix	31%	35%	21%	12%	8%	6%

[1] *Does not include estimates for generic heparin*

[2] *Estimates for Angiomax and Lovenox include uses outside the cath lab*

[3] *Does not include aspirin*

Source: Company data, Morgan Stanley Research

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The New England
Journal of Medicine

VOLUME 346 JUNE 6, 2002 NUMBER 23

A RANDOMIZED COMPARISON OF A SIROLIMUS-ELUTING STENT WITH A STANDARD STENT FOR CORONARY REVASCULARIZATION

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ABSTRACT

Background The need for repeated treatment of restenosis of a treated vessel remains the main limitation of percutaneous coronary revascularization. Because sirolimus (rapamycin) inhibits the proliferation of lymphocytes and smooth-muscle cells, we compared a sirolimus-eluting stent with a standard uncoated stent in patients with angina pectoris.

Methods We performed a randomized, double-blind trial to compare the two types of stents for revascularization of single, primary lesions in native coronary arteries. The trial included 238 patients at 19 medical centers. The primary end point was in-stent late luminal loss (the difference between the minimal luminal diameter immediately after the procedure and the diameter at six months). Secondary end points included the percentage of in-stent stenosis of the luminal diameter and the rate of restenosis (luminal narrowing of 50 percent or more). We also analyzed a composite clinical end point consisting of death, myocardial infarction, and percutaneous or surgical revascularization at 1, 6, and 12 months.

Results At six months, the degree of neointimal proliferation, manifested as the mean (±SD) late luminal loss, was significantly lower in the sirolimus-stent group (−0.01±0.33 mm) than in the standard-stent group (0.80±0.53 mm, P<0.001). None of the patients in the sirolimus-stent group, as compared with 26.6 percent of those in the standard-stent group, had restenosis of 50 percent or more of the luminal diameter (P<0.001). There were no episodes of stent thrombosis. During a follow-up period of up to one year, the overall rate of major cardiac events was 5.8 percent in the sirolimus-stent group and 28.8 percent in the standard-stent group (P<0.001). The difference was due entirely to a higher rate of revascularization of the target vessel in the standard-stent group.

Conclusions As compared with a standard coronary stent, a sirolimus-eluting stent shows considerable promise for the prevention of neointimal proliferation, restenosis, and associated clinical events. (N Engl J Med 2002;346:1773-80.)

THE growing use of stents has improved the results of percutaneous coronary revascularization.[1-5] However, in-stent restenosis continues to limit the long-term success of this approach.[6,7] For example, in a recent randomized comparison of coronary-artery bypass surgery and stenting in patients with multivessel disease, additional revascularization procedures were performed within one year in 21.0 percent of patients who had undergone stenting, as compared with 3.8 percent of patients treated surgically.[8]

In controlled trials, several pharmaceutical agents have failed to inhibit restenosis after coronary interventions.[9] In contrast, the systemic and local delivery of sirolimus (rapamycin), a macrocyclic lactone that inhibits cytokine-mediated and growth-factor–mediated proliferation of lymphocytes and smooth-muscle cells, reduced neointimal proliferation in studies in animals and in a small clinical study.[10-12] We conducted a study to compare the performance of a coronary stent that slowly releases sirolimus over a period of 30 days with that of a standard uncoated stent.

METHODS

Selection of Patients

The study was a randomized, double-blind trial performed at 19 medical centers (listed in the Appendix). It was approved by

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*The members of the RAVEL (Randomized Study with the Sirolimus-Coated Bx Velocity Balloon-Expandable Stent in the Treatment of Patients with de Novo Native Coronary Artery Lesions) study group are listed in the Appendix.

the ethics committee at each participating institution, and all patients gave written informed consent. The study was conducted from August 2000 to August 2001.

Patients were eligible for the study if they were 18 to 85 years old, were not pregnant and were protected against pregnancy during the study, and had received a diagnosis of stable or unstable angina or silent ischemia. Additional eligibility criteria were the presence of a single primary target lesion in a native coronary artery that was 2.5 to 3.5 mm in diameter and that could be covered by an 18-mm stent; stenosis of 51 to 99 percent of the luminal diameter, as estimated visually; and a flow rate of grade 1 or higher according to the classification of the Thrombolysis in Myocardial Infarction (TIMI) trial. Patients were not eligible for enrollment if they had an evolving myocardial infarction, stenosis of the left-main coronary artery, unprotected by a graft, that caused luminal narrowing of 50 percent or more, an ostial lesion, a calcified lesion that could not be completely dilated before stenting, an angiographically visible thrombus within the target lesion, a left ventricular ejection fraction of less than 30 percent, or an intolerance of aspirin, clopidogrel, ticlopidine, heparin, stainless steel, or contrast material.

The Sirolimus-Eluting Stent

Sirolimus was blended in a mixture of nonerodable polymers, and a layer of sirolimus–polymer matrix with a thickness of 8 μm was applied to the surface of a stainless-steel, balloon-expandable stent (Bx Velocity, Cordis, Johnson & Johnson). The stent was loaded with a fixed amount of sirolimus per unit of metal surface area (140 μg of sirolimus per square centimeter). A layer of drug-free polymer was applied on top of the drug–polymer matrix as a diffusion barrier to prolong the release of the drug. The stent was designed to release approximately 80 percent of the drug within 30 days after implantation.

Study Procedures

Codes for random assignments to the treatment groups were generated by computer in blocks of four and were distributed in sealed envelopes to each participating center. Patients were randomly assigned to the groups in a 1:1 ratio.

Lesions were treated with the use of standard interventional techniques. Stenting without predilation was prohibited. After successful predilation, patients were randomly assigned in a double-blind fashion to receive a standard uncoated stent or a sirolimus-eluting stent mounted on a rapid-exchange delivery system and inflated to 10 to 16 atm. The sirolimus-eluting stents were indistinguishable, except under a microscope, from the uncoated stents. After the stent had been implanted, further dilation was performed as necessary to ensure that there was less than 20 percent residual stenosis, with a TIMI grade III flow rate. In case of dissection or incomplete coverage of the lesion, additional stents of the same type as the assigned stent (coated or uncoated) were used.

Intravenous boluses of heparin were administered to maintain an activated clotting time that exceeded 250 seconds during the procedure and were discontinued within 12 hours. Treatment with aspirin, at a dose of at least 100 mg per day, was begun 12 hours before the procedure and continued indefinitely. A loading dose of 300 mg of clopidogrel was administered 48 hours before the procedure, followed by 75 mg daily for eight weeks. Alternatively, treatment with ticlopidine, at a dose of 250 mg twice daily, was begun one day before the procedure and continued for eight weeks. A successful procedure was defined as the successful implantation of the study device, with stenosis of less than 20 percent of the vessel diameter and no major cardiac events during the hospital stay.

Follow-up

Patients were evaluated at 30 days and at 6 and 12 months. They were asked specific questions about the interim development of angina, according to the Canadian Cardiovascular Society classification of stable angina[15] and the Braunwald classification of unstable angina.[16] The patients were also monitored for major cardiac events and for the need for additional revascularization of the index target lesion. An electrocardiogram was obtained at each visit, and an angiographic study was performed at a mean (±SD) of 180±30 days. Other studies and tests were performed at the discretion of the investigators at the participating centers. Because of the double-blind nature of the study, the decision to perform further revascularization of the target lesion or vessel after the six-month angiographic study was also left to the investigators' discretion.

Quantitative Coronary Angiographic Evaluation

Coronary angiograms were obtained in multiple views after the intracoronary injection of nitrates. Quantitative analyses of all angiographic data before, during, and after the procedure were performed by an independent core laboratory (Cardialysis, Rotterdam, the Netherlands) with the use of edge-detection techniques. The luminal diameter of the coronary artery and the degree of stenosis were measured before dilation, at the end of the procedure, and at six months. Restenosis was defined as stenosis of 50 percent or more of the luminal diameter. Late luminal loss was defined as the difference between the minimal luminal diameter immediately after the procedure and the diameter at six months. The target lesion was defined as the stented segment plus the 5-mm segments proximal and distal to the stented segment.

Intravascular Ultrasound Substudy

At the six-month visit, intravascular ultrasound examinations were performed by six centers in subgroups of 48 patients who had received a sirolimus-eluting stent and 47 who had received an uncoated stent.

Study End Points

The primary angiographic end point was in-stent luminal late loss, as determined by quantitative angiography. Secondary end points included the percentage of in-stent stenosis of the luminal diameter, the rate of restenosis (luminal narrowing of 50 percent or more), and the minimal luminal diameter of the stented segment and of the 5-mm segments proximal and distal to the stent at six months.

The primary clinical end point of the study was a composite of major cardiac events, including death, Q-wave or non–Q-wave myocardial infarction, coronary-artery bypass grafting, and revascularization of the target lesion or vessel 30 days, 6 months, and 12 months after the index procedure. A non–Q-wave myocardial infarction was defined by an increase in the creatine kinase level to more than twice the upper limit of the normal range, accompanied by an increased level of creatine kinase MB, in the absence of new Q waves on the surface electrocardiogram.

The end points were adjudicated by an independent clinical-events committee. In addition, a data and safety monitoring board that was not affiliated with the study sponsor reviewed the data to identify any safety issues related to the conduct of the study.

Statistical Analysis

We calculated that with a sample of 207 patients, the study would have 90 percent power to detect a difference in the mean late luminal loss of 0.25 mm between the two groups, assuming a standard deviation of 0.55 mm in each group, with the use of a two-group t-test and a two-sided significance level of 0.05.

All analyses were based on the intention-to-treat principle. For continuous variables, differences between the treatment groups were evaluated by analysis of variance or Wilcoxen's rank-sum test. For discrete variables, differences were expressed as counts and percentages and were analyzed with Fisher's exact test.

Revascularization of the target lesion or vessel and the composite of major adverse events during follow-up were analyzed by the

Kaplan–Meier method. Differences between the event-free survival curves for the two groups were compared with the use of the Wilcoxon and log-rank tests.

All listed authors participated in the study design, enrollment of patients, and data interpretation. The data were held by the core laboratory (Cardialysis, Rotterdam, the Netherlands), but all investigators had full access to them.

RESULTS

Characteristics of the Patients

Between August 2000 and January 2001, 120 patients were randomly assigned to receive the sirolimus-eluting stent, and 118 were assigned to receive the standard stent. With the exception of a significantly higher percentage of men in the standard-stent group, the two groups were similar with respect to all variables examined (Table 1). Overall, 76 percent of the patients were men, and the mean age was 60.7 years, with the expected prevalences of dyslipidemia, diabetes, hypertension, and current tobacco use. Stenting was performed because of unstable angina in 50 percent of the patients. The target vessel was the left anterior descending coronary artery in 50 percent of the patients, the right coronary vessel in 27 percent, and the left circumflex artery in 23 percent. Nearly all the treated lesions were class B1 or B2 according to the American College of Cardiology–American Heart Association classification. Although all the target index lesions were primary lesions, 1.7 percent of the patients had undergone previous coronary-artery surgery and 18.1 percent had undergone previous percutaneous interventions for the treatment of other lesions.

Procedural Characteristics

The lesions in the two groups were treated similarly with the use of conventional techniques. Platelet glycoprotein IIb/IIIa inhibitors, the use of which was left to the discretion of the investigators at the participating centers, were administered to 10.1 percent of the patients in the sirolimus-stent group and 9.5 percent of those in the standard-stent group. The two groups did not differ significantly with respect to the

TABLE 1. BASE-LINE CHARACTERISTICS OF THE OVERALL PATIENT POPULATION AND OF EACH TREATMENT GROUP.*

CHARACTERISTIC	ALL PATIENTS (N=238)	SIROLIMUS STENT (N=120)	STANDARD STENT (N=118)
Age (yr)	60.7±10.4	61.8±10.7	59.7±10.1
Male sex (%)	76	70	81
Previous myocardial infarction (%)	36	38	34
Diabetes mellitus (%)	19	16	21
Treated hypercholesterolemia (%)	40	38	43
Treated hypertension (%)	61	62	61
Current smoker (%)	30	27	33
Angina pectoris (%)†			
Unstable	50	48	52
Stable	39	41	37
Silent ischemia (%)	11	11	11
Target coronary artery (%)‡			
LAD	50	49	51
RCA	27	27	27
LCX	23	24	22
Lesion type (%)§			
A	6	8	4
B1	37	38	35
B2	57	54	61
Reference diameter of the vessel (mm)	2.62±0.53	2.60±0.54	2.64±0.52
Length of lesion (mm)	9.58±3.25	9.56±3.33	9.61±3.18

*Plus–minus values are means ±SD. There were no significant differences between the treatment groups except for male sex ($P=0.05$).

†Unstable angina was defined according to the Braunwald classification,[14] and stable angina according to the classification of the Canadian Cardiovascular Society.[15]

‡LAD denotes left anterior descending coronary artery, RCA right coronary artery, and LCX left circumflex artery.

§The classification of the American College of Cardiology–American Heart Association was used.

rate of successful stent placement (96.6 percent in the sirolimus-stent group and 93.1 percent in the standard-stent group).

Quantitative Angiographic Analysis

Angiographic data at six months were available for 211 of the 238 patients (88.7 percent). The mean reference diameter of the target vessel and the mean length of the lesion at base line were similar in the two groups (Table 1). The mean minimal luminal diameter of the stented segment and the length of the lesion before and after the procedure, as well as the reduction in stenosis immediately after the procedure, were also similar in the two groups (Table 2). At six months, however, the mean minimal luminal diameter of the stented segment was significantly greater in the sirolimus-stent group. The mean in-stent late loss, percentage of stenosis, and percentage of patients with 50 percent or more stenosis were −0.01 mm, 14.7 percent, and 0 percent, respectively, in the sirolimus-stent group, as compared with 0.80 mm, 36.7 percent, and 26.6 percent, respectively, in the standard-stent group ($P<0.001$ for each comparison). Figure 1 shows the cumulative frequency of stenosis immediately after the index procedure and at six months in each treatment group. Table 2 shows the results of subsegmental quantitative angiographic analyses. The late luminal loss at both the proximal and the distal edges of the stent was significantly less in the sirolimus-stent group than in the standard-stent group ($P<0.001$ for both comparisons). There was a small degree of restenosis at the edges of the standard stent that was not present with the sirolimus-eluting stent.

In the subgroup of patients with diabetes, 19 patients received sirolimus-eluting stents, and 25 received standard stents. The minimal luminal diameter before and after stenting was similar in the two groups (0.99 mm in the sirolimus-stent group and 0.93 mm in the standard-stent group before the procedure and 2.37 and 2.36 mm, respectively, afterward). However, at six months, the minimal luminal diameter was markedly larger in the sirolimus-stent group (2.29 mm, vs. 1.56 mm in the standard-stent group; $P<0.001$); consequently, the late loss was smaller (0.07 mm in the sirolimus-stent group vs. 0.82 mm in the standard-stent group, $P<0.001$) and the restenosis rate was lower (0 percent vs. 41.7 percent, $P=0.002$).

Intravascular Ultrasound Evaluation

At six months, intravascular ultrasound examination showed no significant differences between the two groups with respect to the volume of the stent, the volume of the overall vessel, or the volume of the plaque behind the stent. However, the sirolimus-stent group had significantly less neointimal hyperplasia than did the standard-stent group (2±5 vs. 37±28 mm^3) and significantly less volume obstruction, defined as the ratio of the volume of hyperplasia to the volume of the stent, multiplied by 100 (1±3 percent vs. 29±20 percent) ($P<0.001$ for both comparisons). These findings are consistent with the

Table 2. Results of Subsegmental Quantitative Angiographic Analysis.*

Variable	Proximal Edge			Stented Segment			Distal Edge		
	Sirolimus stent	Standard stent	P value	Sirolimus stent	Standard stent	P value	Sirolimus stent	Standard stent	P value
Mean diameter (mm)									
Before procedure	2.66±0.59	2.62±0.58		—	—		2.33±0.55	2.41±0.58	
After procedure	2.78±0.55	2.78±0.53		2.83±0.41	2.82±0.40		2.45±0.47	2.50±0.52	
At 6 mo	2.73±0.59	2.55±0.60	<0.05	2.88±0.48	2.23±0.50	<0.001	2.50±0.53	2.43±0.52	
Minimal luminal diameter (mm)									
Before procedure	2.27±0.60	2.23±0.66		0.94±0.31	0.95±0.35		1.97±0.54	2.07±0.59	
After procedure	2.47±0.53	2.46±0.54		2.43±0.41	2.41±0.40		2.13±0.47	2.21±0.51	
At 6 mo	2.41±0.58	2.19±0.64	0.01	2.42±0.49	1.64±0.59	<0.001	2.20±0.51	2.12±0.51	
Stenosis (% of luminal diameter)									
Before procedure	15.2±9.1	16.2±12.2		63.6±10.7	64.0±10.2		15.9±9.4	14.6±9.8	
After procedure	11.4±5.0	12.1±5.2		11.9±5.9	14.0±6.8	<0.05	13.0±5.2	11.7±5.1	0.057
At 6 mo	12.2±4.7	15.4±8.4	<0.001	14.7±7.0	36.7±18.1	<0.01	12.2±4.9	13.2±6.9	
Late loss (mm)†	0.05±0.39	0.29±0.48	<0.001	−0.01±0.33	0.80±0.53	<0.001	−0.09±0.30	0.12±0.44	<0.001
≥50% restenosis (% of patients)	0	0		0	26.6	<0.001	0	0	

*Plus–minus values are means ±SD.

†Late loss was defined as the difference between the minimal luminal diameter immediately after placement of the stent and the minimal luminal diameter at six months. The data are for patients for whom both post-procedural and follow-up measurements of the minimal luminal diameter were available.

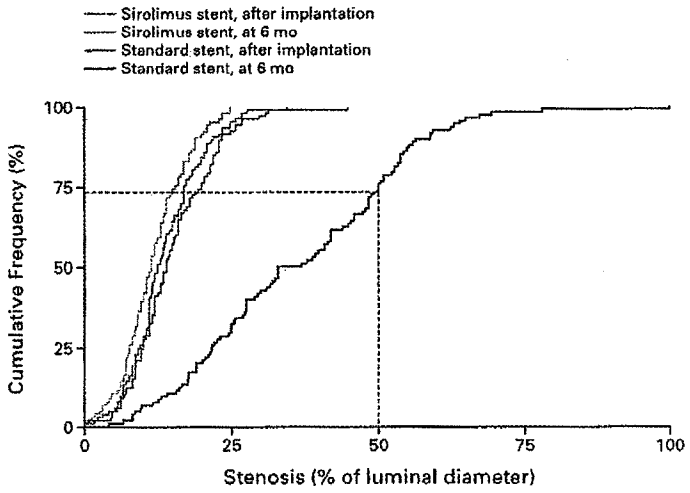

Figure 1. Cumulative Frequency of Stenosis Immediately after Stenting and at Six Months in Patients Who Received Sirolimus-Eluting Stents and in Those Who Received Standard Stents.

The broken lines indicate the percentage of lesions with restenosis (above the line, 22.9 percent) and without restenosis (below the line, 77.1 percent) according to the study definition.

nearly complete suppression of in-stent neointimal hyperplasia by sirolimus. In addition, there was no evidence of an "edge effect," aneurysm formation, in-stent thrombosis, or persistent dissection.

Adverse Events

Major cardiac events are listed in Table 3. Three patients in each group had a myocardial infarction at the time of stenting. In the sirolimus-stent group, two of the patients with myocardial infarction underwent angiography in the hospital, which showed a patent stent in each. The third patient had a non–Q-wave myocardial infarction, and the angiographic study performed at six months showed a patent stent. One recipient of a standard stent underwent further percutaneous revascularization of the target vessel for the treatment of a lesion other than the index lesion.

During a follow-up period of up to one year, two patients in the standard-stent group (1.7 percent) died: one had a myocardial infarction and died suddenly several weeks later, and the other had a gastric hemorrhage. Two patients in the sirolimus-stent group (1.7 percent) also died: one had a subarachnoid hemorrhage, and the other had gastrointestinal cancer. One patient in each group underwent surgical revascularization of the index target vessel.

Percutaneous revascularization of the target lesion was performed in 27 recipients of standard stents (22.9 percent) but in none of the recipients of sirolimus-eluting stents ($P=0.001$). Subacute or late thrombotic occlusion of the stent did not occur in either group.

Kaplan–Meier estimates of event-free survival are shown in Figure 2. The overall rate of major cardiac events was 5.8 percent in the sirolimus-stent group and 28.8 percent in the standard-stent group ($P<0.001$). The difference between the two groups was entirely due to the greater need for repeated revascularization of the target vessel in the standard-stent group. No adverse effects were attributable to the sirolimus coating of stents.

DISCUSSION

We found that use of a sirolimus-eluting stent resulted in the virtual elimination of in-stent neointimal hyperplasia; thus, there was no angiographic evidence of restenosis and no need for repeated interventions. Since the introduction of angioplasty, restenosis has been a major factor limiting the long-term success of percutaneous coronary revascularization.[15] The refinement of stenting techniques in the past decade has substantially improved the overall results of the procedure.[3,4,16,17] Despite considerable efforts to prevent the development of restenosis, however, including systemic or local delivery of biochemical substanc-

TABLE 3. CARDIAC EVENTS IN THE HOSPITAL AND DURING ONE YEAR OF FOLLOW-UP.

EVENT	SIROLIMUS STENT (N=120)	STANDARD STENT (N=118)
Before discharge		
Death — no.	0	0
Myocardial infarction — no.	3	3
Q-wave	2	1
Non–Q-wave	1	2
Coronary-artery bypass grafting — no.	0	0
After discharge		
Death — no.	2	2*
Myocardial infarction — no.	1	2
Q-wave	0	0
Non–Q-wave	1	2
Coronary-artery bypass grafting	1†	1
Percutaneous revascularization of target lesion — no.	0	27
Total — no. (%)	7 (5.8)	34 (28.8)‡
Cumulative event-free survival — %	94.1	70.9§

*Both patients had had previous myocardial infarctions.

†Coronary-artery bypass grafting was performed to treat progressive disease of the left main coronary artery and the ostium of the anterior descending coronary artery, not the target lesion.

‡P<0.001 for the comparison between the two groups with the use of Fisher's exact test.

§P<0.001 for the comparison between the two groups with the use of the log-rank test.

es and drugs[9] and the use of various devices,[18-22] additional target-vessel revascularization is required in more than 15 percent of patients.[8,23] Although catheter-based brachytherapy is effective in the treatment of in-stent restenosis,[24] its value in the treatment of primary lesions is less clear. Furthermore, the use of brachytherapy is limited by its high cost and burdensome instrumentation and by the risks inherent in the use of radioisotopes.

In this context, the benefit of the sirolimus-eluting stent in our study was particularly striking. This new device appears to have virtually eliminated the development of neointimal proliferation. Yet its use did not require special implantation techniques or instrumentation and was innocuous within the time frame of the study.

In the group of patients with sirolimus-eluting stents, the percentage of stenosis at six months was essentially the same as that immediately after the procedure and was in all cases less than 35 percent. The virtual absence of late loss in the luminal diameter in this group is consistent with the arrest of in-stent neointimal proliferation by sirolimus. Also noteworthy was the absence of restenosis and major cardiac events in the patients with diabetes who received sirolimus-eluting stents. Whether these effects can be sustained for several years remains to be determined. The results thus far suggest that the use of an appropriate therapeutic agent when growth-factor–induced cell proliferation is at its peak can have substantial effects on the process of in-stent restenosis.

Sirolimus, a macrolide antifungal agent with a

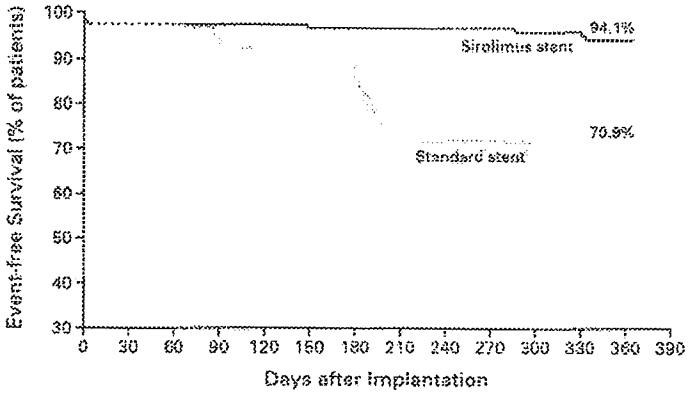

Figure 2. Kaplan–Meier Estimates of Survival Free of Myocardial Infarction and Repeated Revascularization among Patients Who Received Sirolimus-Eluting Stents and Those Who Received Standard Stents.

The rate of event-free survival was significantly higher in the sirolimus-stent group than in the standard-stent group (P<0.001 by the Wilcoxon and log-rank tests).

unique antiproliferative mode of action and powerful immunosuppressant properties, inhibits several regulators of cell-cycle progression and the migration of vascular smooth-muscle cells.[25] Yet studies in animals have shown that reendothelialization may occur even while sirolimus is being eluted.[26] Moreover, recent experiments in animals have shown that sirolimus blocks inflammation.[26] These antiproliferative, antimigratory, and antiinflammatory properties are responsible for the efficacy of sirolimus therapy in preventing acute rejection of renal allografts and arteriopathy of cardiac allografts, as well as in-stent restenosis. The wide safety margin of sirolimus[27] and the minuscule amounts of drug released into the blood explain the absence of detectable adverse effects in our trial and in a previous clinical study.[13]

The restenosis rate of 27 percent in the standard-stent group may seem high. However, on the basis of a linear regression model derived from the Stent Restenosis Study and the Benestent I and II studies (unpublished data), the predicted rate of restenosis for our patient cohort was approximately 28 percent. Of the 27 patients in the standard-stent group who underwent revascularization of the target vessel (22.9 percent), 16 did so because of angina or abnormal stress tests and 11 because of angiographic evidence of restenosis.

Despite the absence of late luminal loss in the sirolimus-stent group, reendothelialization presumably occurred, since none of the patients in the group had acute, subacute, or late thrombosis, even though they received combined antiplatelet therapy for only two months. These findings are similar to reported observations in animals.[26]

We enrolled patients with single lesions that were up to 18 mm long. Whether the positive results in these patients can be expected in patients with more complex or more extensive disease remains to be determined. However, a subgroup analysis showed that the results in patients with diabetes were similar to those in patients without diabetes.

In this trial, 2.5-mm stents were used in 18 percent of the patients randomly assigned to the sirolimus-stent group. Furthermore, division of the treatment groups into thirds according to the vessel diameter revealed virtually identical late luminal loss, even in the smallest arteries.

Stents that deliver drugs are complex devices with three components: the stent, the drug, and the coating. The long-term outcome of treatment with these devices will depend on the response to all three components.

In conclusion, patients with angina who received sirolimus-eluting stents for the treatment of single, primary lesions in native coronary arteries had no angiographic evidence of late luminal loss or in-stent restenosis at six months, no episodes of thrombosis, and a very low rate of cardiac events at one year.

Supported by a grant from Cordis, a Johnson & Johnson company.
Dr. Falotico is an employee of Cordis.

We are indebted to Drs. Rodolphe Ruffy, Brian Firth, and Dennis Donohoe for their assistance in drafting and reviewing the manuscript.

APPENDIX

The following investigators and institutions participated in the RAVEL study: Steering Committee — M.C. Morice (chairperson), Massy, France; P.W. Serruys (cochairperson), Rotterdam, the Netherlands; K. Nijssen, Rotterdam, the Netherlands; C. Bode, Freiburg, Germany; P. Barragan, Marseilles, France; and M. Delattre, Waterloo, Belgium; Sponsor — Cordis, Johnson & Johnson, Warren, N.J., E. Wölfert (program coordinator) and C. Demeyere, Waterloo, Belgium; Data and Safety Monitoring Board — J.G.P. Tijssen, Amsterdam, G. Steg, Paris, and P. Vranckx, Rotterdam, the Netherlands; Data Management — Cardialysis, Rotterdam, the Netherlands; Clinical Events Committee — J. Deckers (chairperson), Rotterdam, the Netherlands; J.A.M. te Riele, Breda, the Netherlands; and L.Q.P.M. van Zeijl, Rotterdam, the Netherlands; Core Angiographic Laboratory — C. Disco, K. Nijssen, and A. Spieringa, Cardialysis, Rotterdam, the Netherlands; Clinical sites — M.C. Morice, T. Lefèvre, and Y. Louvard, Institut Cardiovasculaire Paris Sud, Massy, France; P.W. Serruys, M. van den Brand, D. Foley, W. van der Giessen, P. de Feyter, P. Smits, and J. Vos, Thoraxcentrum, Rotterdam, the Netherlands; C. Bode, M. Rave, and C. Bohlbarsch, Albert Ludwigs Universitätskliniken, Freiburg, Germany; P. Barragan, J.B. Simeoni, C.G. Roquebert, and P. Commeau, Clinique Beauregard, Marseilles, France; G. Schuler, P. Sick, and M. Woinke, Herzzentrum, Leipzig, Germany; G.J. Laarman and F. Kiemeney, Onze Lieve Vrouwe Gasthuis, Amsterdam; W. Wijns, B. de Bruyne, J. Bartunek, P. de Bruyne, G.R. Heyndrickx, Onze Lieve Vrouwe Kliniek, Aalst, Belgium; J. Pajader, J. Marco, B. Farah, P. Sousa, and M. Buccalatte, Clinique Pasteur, Toulouse, France; J.L. Guermonprez, Hôpital Européen Georges Pompidou, Paris; A. Colombo, C. di Mario, R. Albiero, and N. Corvaja, Centro Cuore Columbus, Milan, Italy; A. Bartorelli, S. Galli, F. Fabbiocchi, P. Montorsi, D. Trabattoni, and A. Lualdi, Centro Cardiologico Monzino, Milan, Italy; G. Guagliumi, O. Valsecchi, M. Tespili, A. Vassileva, and A. Saimo, Ospedali Riuniti di Bergamo, Bergamo, Italy; F. Molnár, R.G. Kiss, L. Major, and G. Bokori, Semmelweis Egyetem Egészségtudományi Kar, Budapest, Hungary; E. Bao Hayashi, J. Sanchez, J. Gaspar, R. Villavicencio, and M.A. Peña Duque, Instituto Nacional de Cardiología, Mexico City, Mexico; J.E. Sousa, F. Sousa, A.S. Abizaid, A. Abizaid, A. Sousa, F. Feres, L.A. Mattos, M. Coats, and R. Staico, Instituto Dante Pazzanese de Cardiologia, São Paulo, Brazil; M. Perin, E. Ribeiro, E. Martinez, P. Soares, and F. Bonvartino, University Hospital of São Paulo, São Paulo, Brazil; D. Blanchard and O. Bar, Clinique Saint-Gatien, Tours, France; A. Cribier, H. Eltchaninoff, Centre Hospitalier Universitaire de Rouen, Rouen, France.

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CORRECTION

Sirolimus-Eluting Coronary Stents

To the Editor: The results of the RAVEL study (Randomized Study with the Sirolimus-Coated Bx Velocity Balloon-Expandable Stent in the Treatment of Patients with de Novo Native Coronary Artery Lesions) (June 6 issue)[1] are promising and bring to light the ethical and financial dilemma that is likely to surface once drug-eluting stents are approved for general use. The projected cost of each stent is likely to be about $3,200. Of course, from a financial and societal standpoint, it will not be possible to deploy drug-eluting stents in every case of percutaneous coronary-stent intervention. From an individual patient's standpoint, a drug-eluting stent may be a panacea for a given treated lesion. How does one arrive at a balance? In what cases should the use of a drug-eluting stent be considered absolutely justified and maybe even crucial? We need to arrive at guidelines to determine the point at which the cost of the device offsets the need for repeated coronary interventions, especially in situations in which the risk of restenosis is high or in which presentation with restenosis will probably result in coronary-artery bypass surgery. For example, in patients with diabetes who have a long diseased segment in a small-caliber, proximal left anterior descending artery, treatment with a drug-eluting stent may make good sense. However, a focal lesion in a large-caliber, distal right posterolateral branch in a nondiabetic, nonsmoking patient may not justify the use of a drug-eluting stent.

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1. Morice M-C, Serruys PW, Sousa JE, et al. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. N Engl J Med 2002;346:1773-1780.

Dr. Morice replies:

To the Editor: Sharma and colleagues raise a crucial issue. The cost of drug-eluting stents is indeed very high. However, this high initial cost is expected to be significantly offset by the reduced rate of recurrent events and the subsequent reduced need for repeated intervention observed in our study at one year among the recipients of sirolimus-eluting stents. The cost-effectiveness analysis that was an objective of the RAVEL trial should provide a clearer picture of the financial aspects of the use of these new devices. As they are increasingly used, the price of these stents is likely to decrease, as is often the case with any new device.

In the meantime, the frustration felt by physicians and their patients in view of the financial dilemma rightfully underlined by Sharma et al. seems more than justified. Nevertheless, the spectacular therapeutic progress brought about by the drug-eluting stents is a reality that cannot be denied.

The following RAVEL investigators were inadvertently omitted in the Appendix to our article: C.R. Costantini, M. de Freitas Santos, S.G. Tarbine, D.A. Zanerttini, and J.L. Lazarte, Clínica Cardiológyca C. Costantini, Curitiba Perané, Brazil.

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